Tubulovillous Adenomas with Serrated Features Are Precursors to KRAS Mutant Colorectal Adenocarcinoma

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Conventional adenomas and serrated polyps represent precursor lesions to two separate pathways of colorectal cancer. Occasionally, tubulovillous adenomas (TVA) show focal features resembling traditional serrated adenomas, including ektocytic crypt foci, luminal serration, and cytoplasmic eosinophilia. The biologic significance and molecular findings associated with this histologic variant of TVA are largely unknown.

The goal of this study was to investigate the frequency of KRAS and BRAF mutations in TVA with serrated features (sTVA) in comparison to a control group of TVA.

**Design:** 27 consecutive sTVA and a control group of 27 TVA matched for highest degree of concurrent dysplasia/carcinoma were evaluated. Somatic variants were identified by dideoxy sequencing (assay limit of detection 15%).

**Results:** The mean age of the sTVA group was 68.9 (M F: 1.5:1) and mean age for the TVA group was 63.0 (M F: 1:1.1). All 27 TVA were wild type for BRAF mutation. One sTVA (3.7%) was positive for the BRAF V600E mutation. KRAS analysis was performed on 22 TVA and 24 sTVA. sTVA were significantly more likely to harbor KRAS mutations (66.7% vs. 18.2%, p<0.001). A summary of the KRAS mutations is shown in Table 1. When cases in which KRAS testing was not completed were excluded, there was still no significant difference in the distribution for the highest grade of concurrent neoplasia in the sTVA and TVA groups (p=0.67).

**Conclusions:** We confirm results of few prior studies showing more frequent KRAS mutation in sTVA versus TVA. However, we addressed the shortcoming of prior studies by controlling for the degree of associated dysplasia/carcinoma in our design. KRAS mutation is a molecular correlate of the mixed histology of sTVA and may explain the literature’s tenuous data suggesting a higher risk of advanced outcomes in these polyps.

### Table 1: Summary of KRAS mutations in TVA and sTVA

| KRAS 12/13 Genotype | TVA (n=27) | sTVA (n=24) |
|---------------------|-----------|-------------|
| G12D                | 0 (0%)    | 0 (0%)      |
| G12R                | 4 (16.7%) | 4 (16.7%)   |
| G12S                | 0 (0%)    | 3 (12.5%)   |
| G12V                | 1 (4.5%)  | 5 (21%)     |
| G13C                | 1 (4.5%)  | 1 (4%)      |
| G13D                | 1 (4.5%)  | 5 (21%)     |
| WT                  | 18 (62%)  | 8 (33.3%)   |

**Legend:** TVA-tubulovillous adenoma; sTVA-tubulovillous adenoma; WT-wild type

**Conclusions:** We confirm results of few prior studies showing more frequent KRAS mutation in sTVA versus TVA. However, we addressed the shortcoming of prior studies by controlling for the degree of associated dysplasia/carcinoma in our design. KRAS mutation is a molecular correlate of the mixed histology of sTVA and may explain the literature’s tenuous data suggesting a higher risk of advanced outcomes in these polyps.

**Age Less Than Forty is Predictive of Mismatch Protein Loss in Colorectal Tubulovillous Adenomas

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**Background:** Lynch Syndrome (LS) is a genetic syndrome driven by germline mutations in mismatch repair (MMR) genes. LS is associated with a high risk of colorectal cancer (CRC) at a young age. However, the molecular pathology of colorectal tubulovillous adenomas (TVAs) in LS has not been well characterized.

**Aim:** To investigate the frequency of MMR protein loss in young (<40 years) patients with tubulovillous adenomas (TVAs).

**Methods:** 621 consecutive TVAs were analyzed for MMR expression by immunohistochemistry (IHC) using antibodies against MLH1, MSH2, MSH6, and PMS2. TVAs wereitivity categorized as wild type, MMR positive, or MMR negative.

**Results:** Of the 621 TVAs analyzed, 188 (30.5%) showed MMR protein loss. The average age of MMR negative TVAs was 43.6 ± 16.5 years, while the average age of MMR positive TVAs was 60.2 ± 12.8 years. Among patients under the age of 40 years, 16 (17%) of 94 TVAs showed MMR protein loss compared to 172 (35.3%) of 480 TVAs over the age of 40 years. Six (4%) of 151 tubulovillous adenomas in patients under the age of 40 years showed MMR protein loss, compared to 172 (35.3%) of 480 TVAs over the age of 40 years.

**Conclusions:** Age less than forty is predictive of MMR protein loss in colorectal tubulovillous adenomas. This finding highlights the importance of genetic testing and surveillance in young patients with tubulovillous adenomas.
Design: The study contained 1,426 cases of colorectal cancer, and the primary endpoint was disease-specific survival (DSS). Tumors were classified as either early-stage (T1-2, N0) or advanced-stage (T3-4, N1-3) colorectal cancer. The study compared patients with wild-type KRAS and PIK3CA to those with mutations in these genes. The association between KRAS and PIK3CA mutations and DSS was assessed using Kaplan-Meier survival analysis and Cox proportional hazards regression. *P < 0.05 was considered statistically significant.

Results: Of the 1,426 cases, 1,132 (79.2%) were early-stage and 294 (20.8%) were advanced-stage. KRAS mutations were present in 319 (22.4%) cases, and PIK3CA mutations were present in 294 (20.8%) cases. The 5-year DSS rates were 94.7% for wild-type and 87.4% for mutant KRAS (p = 0.001) and 94.2% for wild-type and 81.8% for mutant PIK3CA (p = 0.001). The median survival time was 102.7 months for wild-type and 35.9 months for mutant KRAS (p < 0.001) and 93.9 months for wild-type and 34.5 months for mutant PIK3CA (p < 0.001).

Conclusions: KRAS and PIK3CA mutations are associated with poor DSS in colorectal cancer. These findings support the hypothesis that KRAS and PIK3CA play a critical role in the development and progression of colorectal cancer.
630** Equivalent CMV Staining by IHC: Frequency and Clinical Significance**
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**Background:** Recent studies examining immunohistochemical (IHC) staining of colorectal biopsies for CMV reported that some cases showed rare small positive nuclei that were called equivocal for CMV. The aim of this study was to determine the extent of equivocal IHC staining for CMV, and whether it is of clinical significance.

**Design:** Out of two-year period, 2014 and 2015, two hundred twenty-five cases of colon and rectal biopsies were stained for CMV by IHC. Slides were reviewed and staining results were recorded as negative when there was completely negative nuclear staining, “equivocal” when at least one large “megalic” nucleus positively stained, and “positive” with only small positively stained nuclei without any positive large (megalic) nuclei. Clinical data were obtained from the medical records.

**Results:** A total of 83 (38%) of the 221 cases showed nuclear staining in at least one cell. Fifty-two cases (24% of all tested, 63% of all positive case) showed equivocal staining. Of these equivocal cases, 4 had completely normal histology, and 9 showed mild nonspecific changes. In the pathology reports, equivocal staining was not recorded in the clinical history. By contrast, only 5 of 356 (1.4%) patients with equivocal staining who did not receive specific treatment improved (p=0.002). Documentation on treatment and/or follow-up was not available for 9 patients with equivocal staining. One of the five patients with equivocal staining who did not respond to antiviral treatment had a flare up of IBD which was not the case for non-negative patients. **Conclusions:** In summary, more patients tested for CMV by IHC show occasional positive small nuclei than classic megalic nuclei, including transplant recipients with normal or minimal nonspecific histology and chronic diarrhea. The majority of these patients respond well to specific antiviral treatment. Therefore 1) all colorectal biopsies from immunosuppressed patients, even with normal histology, should be tested for CMV by IHC and 2) rare small positive nuclei should be reported to the clinicians as positive for CMV.

631** Colonic Carcinomas with Sporadic Loss of Mismatch Repair Proteins Are Associated with Loss of HLA Class I**
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**Background:** The programmed death 1 (PD-1) pathway represses cytotoxic immune responses and protects tumors from the intratumoral T cell infiltrate. Gastrointestinal neoplasms with defective mismatch-repair (MMR) status show dramatic and durable clinical benefit from checkpoint blockade with PD-1 antibodies, however, only half the MSI (microsatellite instability) positive colon carcinomas respond. Herein, we explore three escape mechanisms that may predict resistance to PD1 therapy: 1) absence of PD1L1 expression, 2) absence of PD1 expression, 3) loss of tumor HLA class I proteins. We also validate the immunohistochemical (IHC) assay using a branch chain ISH assay for PD-L1.

**Design:** 96 consecutive colon adenocarcinomas without evidence of Lynch syndrome were evaluated to determine MSI status, PD-L1 reactivity, and HLA Class I antigen expression. MSI status was evaluated on an IHC platform using antibodies against MLH1, PMS2, MSH2 and MSH6. IHC for PD-L1 (clone E131N) and Class I HLA (clone HCL [HCO10]) was performed. In situ hybridization (ISH) for PD-L1 and PD1 (Affymetrix, CA) was performed. The results were validated using TCGA colon cancer dataset.

**Results:** PD-L1 cells express Class I HLA at the advancing edge of the tumor. Tumors with MSI loss were more likely to show loss of HLA class I (MSI loss 29% (7/24), MSI intact 7% (5/72) (p=0.004). PD1L1 IHC was positive in 41% of cases and detected in either macrophages (31%) or tumor cells (9%). PD1-L1 ISH correlated strongly with PD-L1 IHC (Pearson correlation 0.78); ISH signal was noted in either macrophages or tumor cells. Tumors with MMR protein loss were more often positive for PD-L1, in both macrophages and tumor cells (p=0.02); this correlation was validated on the TCGA cohort (p<0.0001). 21% of tumors with loss of MMR proteins expressed PD-L1 in tumor cells compared to 5% in the MSI intact cohort. PD1 positive lymphocytes (> 10/Hpf) correlated with positive PD1L1 staining in neoplastic cells (p=0.03), but not with PD1L1 staining in macrophages (p=0.18). All tumors with PD1-L1 reactivity in neoplastic cells were also positive for PD1 lymphocytes. **Conclusions:** High rate of loss of HLA class I in tumors with sporadic loss of MMR proteins represents a common escape mechanism in this class of tumors and may predict resistance to immunotherapy. IHC analysis of PD-L1 and class I HLA may assist in tailoring checkpoint inhibitor therapy in colonic carcinomas.

632** Albumin RNA In Situ Hybridization in Hepatocellular Carcinomas and Other Neoplastic and Non-Neoplastic Tissue: Can This Be a Clinically Useful Marker?**
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**Background:** RNAsecope is an RNA in situ hybridization (RISH) technology with a unique signal amplification and background suppression strategy. Albumin is a well-known sensitive and specific marker for hepatocellular carcinoma (HCC) but immunohistochemical detection has proven to be difficult practically. With the current use of RISH, we evaluated the efficacy of albumin ISH as a marker of HCC and compared its use in other neoplastic and normal tissues.

**Design:** We evaluated 22 hepatocellular carcinomas (21 whole sections and 1 core in a tissue microarray (TMA)), and neoplastic (12) and non-neoplastic tissue (9) in a TMA with 2 cores each (as shown in Table 1). We performed RISH for albumin using the RNAscope detection kit (Leica Biosystems, Buffalo Grove, IL) with the Bond III autostainer, using probe Hs-ALB-01 (Advanced Cell Diagnostics, Newark, CA). A negative control, DAB, and a positive probe for RNA (PP1B) were also included. Characteristic dot like cytoplasmic reactivity was considered positive. A semiquantitative method of scoring was used: 0 = no staining at all; 1 = <5% tumor cells; 2 = 5-50% tumor cells and 3 = > 50% tumor cells.

**Results:** Albumin RISH was diffusely positive (3+) in 22 of 22 HCCs (figure 1) and 1 neonatal liver.

| Tissue Type          | Albumin RISH Stain Result |
|----------------------|---------------------------|
| Tonsil               | -                         |
| Normal Breast        | -                         |
| Placenta             | -                         |
| Prostate             | -                         |
| Colon                | -                         |
| Skin                 | -                         |
| Splenic              | -                         |
| Salivary gland       | -                         |
| Neonatal Liver       | -                         |
| Breast Carcinoma     | -                         |
| Renal Cell Carcinoma | -                         |
| Medullary Thyroid Carcinoma | - |
| Melanoma             | -                         |
| Pancreatic NET       | -                         |
| Ovarian Carcinoma    | -                         |
| Mesothelioma         | -                         |
| Leydig Cell Tumor    | -                         |
| Thymus               | -                         |
| HCC                  | -                         |
| Papillary Thyroid Carcinoma | - |
| Colon Carcinoma      | -                         |

**All the other neoplastic (12, 100%) and non-neoplastic (9, 100%) were negative.** 10 of 22 HCCs were poorly differentiated carcinomas, all of which were positive for Albumin RISH.

**Conclusions:** In our cohort, Albumin RISH showed a sensitivity of 100% and specificity of 100%. Albumin RISH appears to be a useful marker, also in poorly differentiated HCCs, when other hepatocellular markers may be negative.

633** Peritumoral Lymphoid Cuff in Gastrointestinal Schwannomas Is Significantly Correlated with Regional Lymph Node Enlargement: A Study of 118 Consecutive Cases from a Single Institute**
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**Background:** Primary schwannomas of the gastrointestinal (GI) tract are uncommon subepithelial lesions that usually follow a benign course, although rare cases of malignant transformation have also been reported. The distinction between schwannomas and gastrointestinal stromal tumors (GIST), another subepithelial GI tract tumor, is an important aspect in the preoperative planning of these lesions. One helpful distinction that has been reported is that regional lymphadenopathy (LAD) is more often associated with schwannomas than with GISTs.

**Design:** The Samsung Medical Center pathology database was queried for all resected gastrointestinal schwannomas from January 1998 to June 2016. A total of 118 cases were found.

**Results:** Locations of the lesions varied and included 85 gastric (72%), 11 colonic (9.3%), 7 esophageal (5.9%), 3 pancreatic (2.5%), 1 hepatic (0.8%), and 11 peritoneal (9.3%). The female to male ratio was 1:7.1, and ages ranged from 23 to 80 (mean 55.5) years. The size of the tumors ranged from 0.2 to 11 cm with a mean of 3.8cm. None of GI schwannomas recurred or showed any evidence of malignant transformation. Histologically, in the majority of cases (75 cases - 63.6%), a peripheral lymphoid cuff...
was noted around the schwannoma ranging in thickness from 0.5 to 6 mm (mean 2.8 mm). Regional LAD was assessed through review of prior radiographic and concurrent pathologic findings. Of the 106 cases for which data was available for, 48 cases (45.3%) showed regional LAD. The presence of the lymphoid cuff and regional LAD showed significant positive correlation (p=0.002).

**Conclusions:** Within the GI tract, schwannomas are a rare entity which need to be distinguished from GISTs. The presence of regional LAD favors schwannoma. Histologically, a peripheral lymphoid cuff is seen in the majority of GI tract schwannomas and positively correlates with the presence of regional LAD. However, in a significant subset (36.4%), no lymphoid cuff is present magnifying the importance of correlating preoperative radiologic studies and postoperative pathologic findings in the distinction between GI tract schwannomas and GISTs.

634 Prognostic Significance of Tumour Regression Grade at Primary Site and Its Correlation with Clinical and Histological Parameters in Post Chemotherapy Excision Specimens of Oesophageal-Single Institutional Study

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Background: Carcinoma oesophagus is one of the most lethal malignancies. Surgery is the main treatment modality. Neoadjuvant chemotherapy helps to reduce the tumor burden and increases survival when followed by surgery. Histologic assessment of tumour response-tumour regression grade (TRG), its prognostic significance and correlation with clinical and histological parameters has been extensively studied. The presence of carcinoma oesophagus. This study focuses on correlation of TRG with clinical, histological parameters and survival (DFS/OS).

**Design:** One hundred forty cases of post NACT excision specimens of oesophagus during the year 2014 were retrieved from hospital registry. Follow up details were obtained from electronic medical record. Histology sections were reviewed, TRG was assigned in each case using Mandard grading system. Clinical and histological parameters such as tumour size, site of involvement, histologic type, pTNM stage, circumferential resection margin(CRM), tumour grade and survival were correlated with TRG. Statistical analysis was performed with Kaplan Meier test, log-rank test and Chi square test.

**Results:** Distribution of TRG 1-5 was as follows: TRG 1-26.4%, 2-10%, 3-10%, 4-2% and 5-3.5%. TRG was significantly correlated with pre-chemotherapy size (largest dimension) of the tumour, site of involvement, histologic type, pStage, pN stage and CRM status. TRG was significantly correlated with DFS but not with OS.

**Conclusions:** This study confirms the importance of grading tumour regression in the survival of patients with oesophageal carcinoma with neoadjuvant chemotherapy. It also suggests that TRG should be evaluated in post NACT oesophagectomy specimen.

635 Unique Differential Expression of PD-L1 in Anal Squamous Cell Dysplasia and Invasive Carcinoma

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Background: Analysis of the tumor microenvironment (TME) has served as a promising emerging actionable genomic alteration for which targeted therapy is likely to be developed. Here, we examine the expression pattern of PD-L1 in various subtypes of anal squamous cell carcinoma (SCC). Our data imply a potential benefit for anal SCC patients with IHC expression of PD-L1.

**Materials and Methods:** A total of 42 patients with either in situ and/or invasive anal SCC from 37 unique institutions were included. For all cases with adequate available tumor tissue, PD-L1 expression was evaluated based on staining intensity in either the membrane, cytoplasm or both by IHC. The membrane and cytoplasmic expression were scored independently and the higher of the two scores was utilized for analysis. Positive L1 was performed for all cases with proper positive and negative controls. Positive control was set at 5% IHC staining with the antibody used for staining was evaluated based on staining intensity in either the membrane, cytoplasm or both. The highest intensity staining was scored as 1+. Staining intensity of 1-2+ was considered positive and 3+ was considered strong positive. Staining intensity of 4 was considered equivocal.

**Results:** All 42 cases (100%) displayed HPV-associated diffuse or circumferential staining was evaluated based on staining intensity in either the membrane, cytoplasm or both by IHC. The membrane and cytoplasmic expression were scored independently and the higher of the two scores was utilized for analysis. Positive L1 was performed for all cases with proper positive and negative controls. Positive control was set at 5% IHC staining with the antibody used for staining was evaluated based on staining intensity in either the membrane, cytoplasm or both. The highest intensity staining was scored as 1+. Staining intensity of 1-2+ was considered positive and 3+ was considered strong positive. Staining intensity of 4 was considered equivocal.

**Conclusions:** The association of PD-L1 expression with HPV status in both in situ and invasive SCC, and all cases exhibited scattered p53 positive cells (wild-type p53).

636 RICTOR Overexpression/Amplication in Advanced Head and Neck Tumors: a Correlation Study Utilizing Immunohistochemistry, Fluorescence in Situ Hybridization, and Targeted Sequencing

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Background: RICTOR is a key component of the mTORC2 complex (mTORC2). When activated, this complex promotes cell proliferation and survival through the activation of downstream AGC kinase family members. Amplification of RICTOR serves as a promising emerging actionable genomic alteration for which targeted therapy will likely be developed. However, the incidence of RICTOR amplification in advanced solid tumors is an area that has not been explored.

**Design:** In this study, a multimodal design was used in order to study RICTOR amplification through the use of immunohistochemistry (IHC; n=416), fluorescence in situ hybridization (FISH; n=51) and deep targeted sequencing (n=51) in a number of solid organ tumors including colorectal (n=193), gastric (n=86), renal cell carcinoma (n=94) and other solid cancers (n=103).

**Results:** RICTOR was overexpressed in 202 cases (48.6%): 1+, 30.3%; 2+, 14.4%; 3+, 4.1% by IHC, and amplified in 29 cases (56.9%) by FISH and 24 cases (47.1%) by targeted sequencing. Overexpression/amplification of RICTOR was found in 111 (33%) colorectal cancers, 38 (44.2%) gastric cancers, 16 (47.1%) renal cell cancers, and 37 (35.9%) other tumors. The IHC results were significantly positively correlated with FISH (p<0.001; r=0.66), but no significant correlation was seen between IHC and targeted sequencing (p=0.49).

**Conclusions:** In conclusion, RICTOR overexpression/amplification is fairly common in a variety of advanced solid tumors. Additionally, IHC for RICTOR appears to be a reliable surrogate marker for amplification, which may very well have future therapeutic implications.

637 Low Grade Appendiceal Mucinous Neoplasms with Neoplastic Epithelium Confined to the Appendix: 45 Cases with Clinical Follow-Up

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Background: Appendiceal mucinous neoplasms continue to be a challenge for pathologic classification and clinical management. The World Health Organization (WHO) divides these tumors into three categories: adenoma (low grade dysplastic mucinous epithelium with intact muscularis mucosa), low grade appendiceal mucinous neoplasm (LAMN) (mucin and/or dysplastic epithelium beyond the muscularis mucosa, including extra-appendiceal low grade neoplastic epithelium), or mucinous adenocarcinoma (infiltrative invasion). The anxiety concerning a diagnosis of LAMN in routine clinical practice can be at least partly attributed to the limited number of outcome studies to guide management. This single institutional study will focus on the clinical behavior of 2 subgroups of LAMN: mucin pools and neoplastic epithelium confined by appendicular serosa and cases with acellular mucin alone beyond the appendicular serosa.

**Design:** 104 appendiceal mucinous neoplasms (entirely submitted for histologic evaluation) were retrieved from the pathology database (1990 - 2016). 45 cases met our inclusion criteria (extended follow-up defined as ≥6 months and absence of neoplastic epithelium outside the appendicular serosa).

**Results:** Two subgroups of LAMN were identified: 36 cases with mucin and neoplastic epithelium confined by appendicular serosa and 9 cases with extra-appendiceal low grade neoplastic epithelium confined by acellular mucin. All were managed by either appendectomy (n=34; 4 with partial cecectomy) or mucin pools and neoplastic epithelium confined by appendicular serosa and cases with acellular mucin alone beyond the appendicular serosa.

**Conclusions:** Our study adds to the literature supporting an excellent prognosis with negligible risk of recurrence in cases of LAMN confined within the appendicular serosa. These tumors may be best treated (or even cured) by appendectomy alone. Right hemicolectomy may not be necessary even in cases noted to have low grade mucinous epithelium at margin. Regular follow-up with colonoscopy including observation of the appendix resection site may be a more efficient method of recurrent disease monitoring.

638 Indoleamine 2,3-Dioxygenase 1 (IDO1) Expression in Bilary Tract Cancers

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Background: Indoleamine 2,3-dioxygenase 1 (IDO1) is one of the key rate limiting enzymes involved in tryptophan metabolism through the kynurenine pathway. IDO1 has been shown to exert an immunosuppressive effect in the tumor microenvironment and prevent exaggerated T cell response. Here, we investigate IDO1 as a potential prognostic marker in biliary tract cancer and correlate its expression with clinic-pathological variables.

**Design:** We investigated IDO1 expression by immunohistochemistry in a well-characterized tissue microarray cohort of 161 biliary tract cancer patients. Anti-IDO1
Nestin expression in human PDACs and a possible prognostic marker.

Multiple study showed nestin is a stem cell marker of pancreatic ductal malignancies. Nestin, a class VI intermediate filament protein, detected in neural stem cells, has also been associated with pancreatic cancer. In PDAC, nestin expression is related to tumor progression and may act as a prognostic marker.

Conclusions: Nestin is considered as a stem cell marker which showed prognostic value in animal and cell lines studies. Our study showed that Nestin expression can be detected in a subset of PDACs, and not associated with common prognostic markers.

There is no association among Nestin expression, tumor grade, lymph node status, angioinvasive growth and perineural invasion.

Conclusions: Nestin is considered as a stem cell marker which showed prognostic value in animal and cell lines studies. Our study showed that Nestin expression can be detected in a subset of PDACs, and not associated with common prognostic markers.
ErbB3 Overexpression Predicts Survival in Primary Colorectal Cancer

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Background: ErbB3 is a member of egf receptor (EGFR) family and has dual roles in promoting cellular proliferation and preventing apoptosis through activation of PI3K/AKT pathway. ErbB3 as a heterodimerization partner also promotes tumor invasion and metastasis in many solid tumors. ErbB3 expression and its correlation with the clinical outcome in primary colorectal cancer (CRC) have been assessed in a limited number of studies with contradictory results. We examined ErbB3 expression in a large cohort of primary CRC and assessed its performance as a potential independent prognostic marker.

Design: ErbB3 expression was assessed by immunohistochemistry using tissue microarrays from 128 cases of primary CRC patients (stage I-IV) treated in our institution. Intensity and extent of ErbB3 staining were independently assessed by 2 pathologists on a scale from 0 to 3. Cytoplasmic (c) and membranous (m) ErbB3 staining scores were calculated as a weighted average from 3 core samples per tumor. Univariate analysis of average scores and clinicopathologic outcome measures from patient chart review was completed.

Results: ErbB3 is overexpressed in CRC compared to normal colonic epithelium (n=119; p=0.01). The proportion of positive lymph nodes per case was positively associated with higher membranous and cytoplasmic erbB3 expression level in tumor cells (n=125; p=0.01). Both cytoplasmic and membranous ErbB3 overexpression in tumor cells were associated with improved 2-year survival (n=126; p=0.02 and p=0.03, respectively), but were not associated with conventional prognostic factors such as tumor stage, lymph node involvement and lymphovascular invasion.

Conclusions: Our findings show that ErbB3 overexpression in primary CRC is associated with better 2-year survival. Given the divergent results of the role of ErbB3 expression in primary CRC reported in the literature, standardizing ErbB3 expression analysis would be an important next step in evaluating the role of ErbB3 in CRC prognosis. Increased expression of ErbB3 at the protein level in particular merits further analysis would be an important next step in evaluating the role of ErbB3 in CRC.

Myosin 1e Expression Is Associated with Disease Progression in Colorectal Cancer

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Background: Colorectal cancer (CRC) is the second leading cause of cancer-related death globally. The current histopathological staging paradigms for identifying high-risk patients and predicting chemotherapy benefit is imperfect. As a result, many patients are undertreated, putting them at increased risk for disease relapse, or overtreated, exposing them to unnecessary and harmful chemotherapy with no potential benefit.

Design: We thus analyzed on FFPE whole-tissue sections of 80 CRC, the expression of MYO1E, a long-tailed, class I myosin, regulating endocytosis, adhesion, migration, and invadosomes in kidney podocytes. Despite MYO1E expression in numerous cancers, its association with tumor progression is poorly understood.

Results: The ratio of MYO1E tumor/NAT expression was negatively associated with stage progression and increased invasiveness of tumors characterized by T-score. Moreover, tumors that had to spread to regional lymph nodes had a significantly lower Myo1e expression ratio than tumors localized at the primary site. These data provide clinical evidence that reduced expression of Myo1E, compared to matched NAT, is associated with disease progression.

Conclusions: This study identifies MYO1E as a potential prognostic biomarker in CRC. Further examination of MYO1E expression to predict disease relapse and survival in a large retrospective study of CRC patients is suggested to define its prognostic utility to improve the clinical management of CRC patients.
was only observed in MSI CRC (19/41, 46% with PD-L1 expression in more than 5% of tumor cells - score 3, p < 0.0005). Conversely, PD-L1 expression by immune cells was observed in MSI CRC (23/41, 56% with PD-L1 expression by more than 5% of positive cells) but also in MSS CRC (18/89, 43%) (p = 0.5). The density of PD-1+ cells was significantly correlated to the PD-L1 expression, as well as the density of Tbet+ TIL.

**Conclusions:** PD-L1 expression is 1) heterogeneous in CRC, among CRC but also within the same tumor, 2) preferentially observed in MSI CRC (78%), especially in MSS CRC (18/89, 43%) when PD-L1 is expressed by tumor cells, 3) correlated with the presence of PD-1+ or Tbet+ TIL and 4) observed in a significant proportion of MSS CRC (46%) by immune cells only. From a clinical point of view, PD-L1 expression has to be determined at best in full tissue section and besides its preferential expression in MSI CRC, its significant frequency and expression profile (only by immune cells) in MSS CRC should be taken into account in the future clinical trials testing the efficacy of anti-PD-1/PD-L1 antibodies.

### 647 Frequency of Deficient Mismatch Repair (MMR) Proteins and HNPCC in Patients with Colorectal Carcinoma (CRC) Younger and Older Than or Equal to 70 Years

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**Background:** The 2015 NCCN guidelines recommend screening either all CRC patients or those younger than 70 years old and those 70 years old and older who meet the Bethesda guidelines for HNPCC at the time of diagnosis. It is debatable whether patients 70 years and older with colorectal cancer are less likely to have HNPCC. We analyzed the frequency of MSH high status and HNPCC among these two groups of patients.

**Design:** We retrospectively searched our pathology database for patients who underwent resection, polypectomy and biopsy for CRC from 2013 to 2016. Patient age, gender, tumor site, immunohistochemistry (IHC) result for MMR proteins, and HNPCC status were recorded. IHC for MMR proteins was performed using Ventana kit (MSH1, MSH2, MSH6 and PMS2) and an automated system. Patients who only had MLH1 and PMS2 deficiency with positive BRAF mutation and hypermethylation were defined as low probability of HNPCC, whereas those who had either loss of PM2S2 only, MSH2 and/or MSH6 were classified as high probability of HNPCC. Fischer’s exact test was performed when appropriate.

**Results:** Among 316 patients identified, 191 patients were <70 years old, and 125 patients were >=70 years old. Both groups had almost equal sex distribution (M:F ratio: 1.17:1 and 0.87:1). In the younger age group, the tumor was predominantly right-sided (n=137, 71%), whereas the older age group showed an equal distribution (n=62 vs. n=63). The percentage of loss of MMR proteins detected by IHC in the younger group (19% or 36/191) was not significantly different from that in the older age group (23% or 29/125) (P>0.05). There was also no significant difference between the percentage of patients with high probability of HNPCC in younger and older age groups (8% or 16/191 vs. 2% or 3/125). However, among patients with loss of MMR proteins in the tumor, the younger age group had a significantly higher percentage of high probability of HNPCC (44% or 16/36 vs. 10% or 3/29) (P < 0.05).

**Conclusions:** In our institution, screening by IHC for MMR proteins identified similar frequencies of HNPCC in highly probable HNPCC in younger and older than 70 year old patient groups, supporting universal screening for HNPCC regardless of age. There was no statistically significant difference in the percentage of HNPCC or highly probable HNPCC among the younger group who have loss of MMR proteins in the tumor, suggesting that the loss of MMR proteins in tumors in older patients is more likely an epigenetic event.

### 648 Hirschsprung Disease and Its Mimickers: A Detailed Histomorphological Study of 12 Cases

**Maria Bukalo, Amanda C Pinto, Sarvari Mohanty, P Divya, N B Namdeo, K M Bhaa, Usha Kini. St. John’s Medical College, Bengaluru, Karnataka, India.**

**Background:** Hirschsprung disease (HD) most commonly presents in neonates with abdominal distension and constipation. Their rectal biopsy shows aganglionosis with depleted SMA expression. These features are compatible with the clinical diagnosis of myopathic type of intestinal pseudo-obstruction.

**Conclusions:** Adults presenting with symptoms of abdomen distension and chronic constipation should be evaluated for HD and its variants. Syndromic (MEN2B) and autoimmune variants should be kept in mind. Myopathic cases should be evaluated with a full thickness colonic biopsy. Unlike HD, surgical excision of the abnormal bowel is not advocated as its proximal extent of the pathology is not assessable and hence the management is a challenge.

### 649 Unique Prognostic Significance of CD206 and CD163 Macrophage Subtype Markers in Esophageal Adenocarcinoma

**Weng Cao, Margaret A Black, Jiangzhou Xu. New York University Langone Medical Center, New York, NY; University of Illinois at Chicago, Chicago, IL.**

**Background:** Detection macrophage subtype in tumor microenvironment could be prognostically useful. M2 macrophages are associated with survival advantage in CD163 and CD206 are often used in a variety of tumors to correlate M2-like macrophage in tissue with patient prognosis. Thus we compared the prognostic significance of CD163 or CD206 positive M2 macrophage in esophageal adenocarcinoma (EAC).

**Results:** CD163 cell line STG was used to monocyte into M2 macrophage. RT-PCR was employed to identify its cytokine expression profile. 53 EAC resection specimens were immunostained with CD68, CD163 and CD206. Average numbers of M2 (CD68+/CD163+) or CD68+/CD206+ macrophages were counted at five hot spots in tumor islet and tumor stroma. Compared to EACs without lymph node metastasis, CD206 or CD163 positive M2-like macrophage counts in tumor islet and tumor stroma was not significantly increased in EACs with positive lymph nodes, and did not show a correlation with lymph node metastasis. Interestingly, CD163 positive M2-like macrophage possessed a strong correlation with patient survival independent of location (P<0.05). Counts of CD206- or CD163-like macrophage in EAC was not associated with patient age, gender, tumor size, and tumor differentiation.

**Conclusions:** CD163 is a suitable M2-like macrophage maker for macrophage subtype contributing to EAC progression and prognosis. Data also suggest choosing appropriate M2 macrophage marker is important in related cancer studies.

### 650 Epidemiologic Evaluation of Biopsies Performed for Potential Gastrointestinal Gvhd

**David Carr, Grace Y Lin, Maqin Haoeseci. UC San Diego, San Diego, CA.**

**Background:** Gastrointestinal graft-vs-host disease (GVHD) is an important complication of allogeneic bone marrow transplantation and is common in both its acute and chronic forms. Severe gastrointestinal GVHD is an important diagnostic entity associated with high mortality. With the incidence of bone marrow transplantation increasing, and continued improvement in GVHD prophylactic regimens, a thorough understanding of the presentation and epidemiology of GVHD is crucial.

**Design:** The pathology archives were searched for gastrointestinal biopsies performed when appropriate.

**Results:** 2015 NCCN guidelines recommend screening either all CRC patients or those younger than 70 years old and those 70 years old and older who meet the clinical criteria for EAC progression. Data also suggest choosing appropriate M2 macrophage marker is important in related cancer studies.
fewer than 12 lymph nodes in colonic adenocarcinoma cases is associated with a worse prognosis; this concept has not been explored in GEP NETs. The goal of this study was to determine if the number of examined lymph nodes or the number of positive lymph nodes is associated with prognosis in GEP NET.

**Design:** Our pathology database was searched from 2008-2013 for cases of GEP NET with corresponding lymph node dissection. Tumor characteristics including number of lymph node metastases and number of lymph nodes examined were collected from corresponding pathology reports. Patient outcome data was collected from chart review.

**Results:** The study group consisted of 84 GEP NET from an equal number of patients (38 small bowel/ampullary NET, 33 pancreatic NET (PanNET), 9 colorectal NET, 2 gastric NET, 2 appendiceal NET). The average number of lymph nodes examined per case was 17.8 (range 1-66), the average number of positive lymph nodes per case was 2.4 (range 0-18), and the average lymph node ratio per case was 0.19. PanNET had significantly more lymph nodes examined per case compared to other sites (mean 22.6 vs. 14.6, p=0.002) but the lymph node ratio for PanNET was not significantly different (0.15 vs. 0.22, p=0.02). When all cases were included, disease free survival was not significantly different for cases with <12 lymph nodes examined compared to those with ≥12 lymph nodes examined (p=0.11). Some separation of patients with no lymph node metastases versus those with lymph node metastases on survival curves, although not significant (p=0.37). When positive lymph nodes were divided into 1 or >1, this separation became less pronounced (p=0.53).

**Conclusions:** In these preliminary findings, there is no evidence to suggest that the number of lymph nodes examined or number of positive lymph nodes are associated with disease-free survival for GEP NET. We are building a larger cohort to strengthen our findings.

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**Table 1. Clonal TCR and Follow Up Development of Malignancy**

| Clonal TCR, clone (n, %)     | New CD (n=1) | HP (n=5) |
|-----------------------------|--------------|----------|
| RCD (n=12)                  | 67           | 47       |
| Mean Age (yrs)              | 62           | 47       |
| Gender (female, %)          | 9 (75%)      | 4 (80%)  |
| TCR, clone (n, %)           |              |          |
| 6/12 RCD (50%)              | 2 (18%)      | 2 (40%)  |
| 2 (18%)                     | 2 (40%)      |          |
| Sequential TCR (n=7)        |              |          |
| Multiple clones             |              |          |
| Persistent identical clone  |              |          |
| 2/7                         |              |          |
| Development of Malignancy   |              |          |
| 1 nodal B cell lymphoma     |              |          |

**Conclusions:** Monoclonal T-cell populations are present in patients with RCD, newly diagnosed CD, and HP associated duodenal lymphocytosis. This finding highlights the clinical non-specificity of results of PCR TCR gene rearrangement using paraffin embedded tissue. Test results should be correlated with morphology, sequential biopsies, and clinical status. The finding of monoclonal T-cell populations in conditions of duodenal lymphocytosis is of limited clinical significance as a stand-alone test.

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**653 Dysplasia in Sessile Serrated Polyps Is Frequently Encountered in Patients Meeting Serrated Polyposis WHO Diagnostic Criteria**

**Romulo Celli, Joanna Gibson. Yale Medical School, New Haven, CT.**

**Background:** Serrated polyposis syndrome (SPS) is defined by multiple colonic serrated polyps (SP) and increased risk of colorectal cancer (CRC). The 2010 WHO criteria for SPS are: 1) ≥5 SP proximal to sigmoid; 2) ≥2 being ≥1 cm; 2) any SP proximal to sigmoid in a patient with a 1st-degree relative with SPS or 3 ≥2 SP. SPS incidence is unknown and a confirmatory test is unavailable. We tested the utility of the WHO criteria in identifying patients with SPS in a large cohort.

**Design:** We identified 3245 consecutive patients with at least 1 SP (hyperplastic polyp, HP; sessile serrated polyp, SSP; and traditional serrated adenoma, TSA) were identified via retrospective review of the pathology database over the year 2014. Each patient was screened for SPS and clinicopathologic examination was performed of patients meeting WHO criteria.

**Results:** We identified 32 patients (18 female, mean age 67 years) who met SPS WHO criteria. 3 patients met criteria at the 1st colonoscopy; remaining patients met criteria after tabulating data from a mean of 3.5 procedures. 20 patients met criterion 1 (Group A), 7 met criterion 3 (Group B), and 5 met both 1 and 3. The mean number, size, distribution and histologic type of SP differed significantly between Group A and B (10.5 vs 3.4, p=0.00; 0.77 cm vs 0.41 cm, p=0.00, 29% vs 6% right sided, p=0.00; and 39% vs 16% SSP, p=0.00, respectively). 13% of SPS patients had SSP with advanced neoplasia (SSP-AN), including 1 with high grade dysplasia and 3 with CRC, compared to 0.9% of the non-SPS patients in this cohort. The total number of polyps in patients with SPS-AN was 23, and no patient with SSP-AN had less than 10 polyps.

**Conclusions:** We identified 32 patients meeting SPS criteria among 2345 patients with at least one SP (1.4% incidence). SP histology, size and anatomic distribution varied between patients meeting criteria 1 or 3, confirming other studies. The majority of patients with SSP-AN had SSP with advanced neoplasia (SSP-AN), including 1 with high grade dysplasia and 3 with CRC, compared to 0.9% of the non-SPS patients in this cohort. The total number of polyps in patients with SPS-AN was 23, and no patient with SSP-AN had less than 10 polyps.

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**654 Interobserver Variability in the Diagnosis of Inflammatory Bowel Disease-Associated Dysplasia by International Telepathology**

**Michael Chang, Yantai Huang, Dipan M Karamchandani, Xuan-rui Wu, Daniella Allende, John R Goldblum, Shu-Lian Xiao, Hangfa Zhu, Michael Feeley, Amy Collinsworth, Ashwin K Ennakalala, Hao Xie, Xiali Liu. U of Florida, Gainesville, FL; Penn State U, Hershey, PA; Sun Yat-sen U, Guangzhou, China; Cleveland Clinic, Cleveland, OH; U of Chicago, Chicago, IL; Mount Sinai Hosp, New York, NY; Yale U, New Haven, CT.**

**Background:** Dysplasia arising in association with inflammatory bowel disease (IBD) is the most significant marker of increased colorectal cancer risk in IBD patients. Telepathology (TP), the practice of remote diagnostic consultation, has seen increased use nationally and internationally. The aim of this study was to evaluate the utility and interobserver variability of diagnosing dysplasia in IBD with TP.

**Design:** Eight gastrointestinal (GI) pathologists were involved in this study. A total of 50 colonic biopsies from patients with IBD were included. One representative microscopic slide in each case was digitized using an Aperio system. Photographs of full slide images were captured at low, medium, and high magnifications at a resolution of 1712 x 1072 pixels and saved as tagged image file format (TIFF) files on read-only DVD. Each pathologist selected the most appropriate diagnostic category using the consensus IBD pathology reference slide. Discordance was categorized as Group A and B (10.5 vs 3.4, p=0.00; 0.77 cm vs 0.41 cm, p=0.00, 29% vs 6% right sided, p=0.00; and 39% vs 16% SSP, p=0.00, respectively). 13% of SPS patients had SSP with advanced neoplasia (SSP-AN), including 1 with high grade dysplasia and 3 with CRC, compared to 0.9% of the non-SPS patients in this cohort. The total number of polyps in patients with SPS-AN was 23, and no patient with SSP-AN had less than 10 polyps.

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655 Hydrophilic Polymer Associated Ischemic Enterocolitis
Jeev A Chopra, Wei Chen, Wendy L Frankel, Christina A Arnold. The Ohio State University, Columbus, OH.

Background: Hydrophilic polymer coating of medical devices serves to lubricate the device and prevent device-related complications. The coating can be disrupted and result in downstream pathology via presumed thromboembolism. This process has been reported in the brain, heart, lung, and skin, and has been replicated through animal studies and in vitro histologic processing of the polymer coating. We report the first description of hydrophilic polymer associated ischemic enterocolitis.

Design: Prospective identification of the polymer from gastrointestinal resection specimens from 04/29/2014-08/08/2016 resulted in collection of seven specimens (small bowel=2, colon=4, aortic thrombus=1) from three patients.

Results: We report a 4% incidence of hydrophilic polymer associated ischemic enterocolitis among all patients with an ischemic bowel resection during this study. All patients developed bowel ischemia within one day of aortic repair. All resection specimens showed ischemia, and the polymers were mainly located in the submucosal vessels in areas of ischemia. They appeared as intravascular, serpiginous structures with basophilia. In the patient who developed acute paralysis after the aortic repair, identical polymers were identified in the aortic thrombus and the ischemic bowel segment. We demonstrate that the polymers display an altered morphology over time and with various graft types, and that the degrading polymers are associated with foreign body giant cell reaction. Special stains can be helpful with the polymers tunescing on a colloidal iron, pink on Kossa and mucicarmine, and pale blue on a trichrome. Clinical follow-up was available up to 115 weeks: one patient died, and the other two are alive and well.

Conclusions: In summary, we report a new diagnostic entity to be considered in the differential of atrophic ischemic injuries. Awareness of this entity is important to physicians who treat patients with ischemia and to prevent misdiagnosis of the polymers and their associated giant cell reaction as a parasitic infection, granulomatous vasculitis, sarcoidosis, and idiopathic inflammatory bowel disease.

656 Assessment of PD-L1 Expression in Tumor Microenvironment of Mismatch Repair Deficient Colon Cancer: Comparing Two Antibody Clones, SP142 vs. SP263
Zongming E Chen, Angela Bitting, Fan Lin. Geisinger Medical Center, Danville, PA.

Background: Mismatch repair deficient (MMRD) colon cancer harbors increased number of somatic mutations and is potentially more immunogenic. To evade host immune destruction, the tumor cells utilize check point inhibition mechanisms. Consequently, PD-L1 expression in the tumor microenvironment exhibits prognostic significance in this subtype; and majority patients benefit from anti-PD1 immunotherapy. However, the evaluation of PD-L1 expression may differ depending on different antibody clones. Here, we compared the results using two PD-L1 clones SP142 and SP263.

Design: Immunohistochemistry (IHC) for PD-L1 was performed on 40 MMRD colon adenocarcinomas using tissue microarray sections. The tumors were selected for their potential to elucidate the cause of ischemia and to prevent misdiagnosis of the polymers and the highest and lowest density were counted. Presence of extracellular tryptase was recorded. The number of fragments that showed inflammation were counted in each case to assess the extent of inflammation.

Results: Antigen expression by tumor and immune cells, presence of extracellular tryptase, and extent of inflammation were compared to those of digital automatic quantifications into tumor cell (PD-L1 TC+) and immune cell (PD-L1 IC+) expression by pathologic immunohistochemistry.

Conclusions: The pathogenesis of microscopic colitis is largely unknown and likely to be multifactorial; our findings suggest that mast cells may play a role. Therapies targeting mast cells, especially those that stabilize cell membranes and prevent degranulation, may be effective in these patients, but precluding the need for long term steroid therapy. Evaluation of mast cell numbers, presence of extracellular tryptase, and extent of inflammation might identify patients most likely to respond to such therapies.
was assessed by calculating Manders’ overlap coefficient with threshold set by Costes method (CM) using Fiji (Cars 2 plug-in). We perform cell segmentation using Otsu’s method and define PD-L1 positive cell ratio as an absolute number of positive cells per square millimeter. With pathologic observation, we observed PD-L1 expression in 48 (61.5%) cases consisting 7 (9.0%) PD-L1+ and 41 (53.0%) PD-L1- cases. PD-L1+ cases were frequently associated with higher tumor grade metastasis (p=0.027) and advanced TNM stages (p=0.029). Moreover, PD-L1+ is an independent favorable prognostic factor in overall survival (versus PD-L1−); hazard ratio, 3.45; 95% confidence interval, 1.17-12.745; p=0.025. We found significant correlation between manual and automatic quantification (Pearson r=0.8 and P < 0.001). Spearman test, too, showed significance.

Conclusions: In MSI-high GC, PD-L1 expression in immune cells is independently associated with longer survival.

**660 IgG4-Related Disease of the Gastrointestinal Tract: A Tertiary Care Hospital Experience**
Woo Cheol Cho, Severino Ligato, Richard Cartun, Ansha Trivedi, Hartford Hospital, Hartford, CT.

Background: IgG4-related disease (RD) is a newly recognized rare clinicopathologic entity characterized by dense fibrosis & lymphoplasmacytic infiltration rich in IgG4-positive plasma cells in association with an elevated serum IgG4 level. We report our 10-year experience with IgG4-RD as a tertiary care hospital, with a primary focus on the gastrointestinal tract, & discuss the challenges associated with the diagnosis.

Design: We searched our laboratory database for patients with suspected IgG4-RD encountered over a 10-year period (2006-2016), using the following terms: “IgG4,” “autoimmune pancreatitis,” “autoimmune sclerosing cholangitis,” “retroperitoneal fibrosis,” and “inflammatory pseudotumor.” All slides and electronic medical records were retrospectively reviewed.

Results: The material examined consisted of 11 surgical and 5 biopsy specimens, all of which were histologically confirmed to have IgG4-RD in at least 1 organ. 63% were male and the median age at diagnosis was 60.5 years (range, 15-79). The primary sites in order of frequency were as follows: pancreas (6), mesentery (5), bile duct (3), retroperitoneum (3), & gallbladder (1). Serum IgG4 levels were obtained in 19 (3/16) of patients, all of whom were found to have elevated serum IgG4 levels. In 1 patient, a serum total IgG level was obtained instead, which was elevated at 1852 mg/dl. 13.2% (2/16) of patients had a history of malignancy and 6% (1/16) of patients had another documented autoimmune disease (Sjogren syndrome, RA) or adenocarcinoma (both cases with IgG4-related sclerosing pancreatitis, 33.3% (2/6) of them had a history of alcohol abuse. 13% (2/16) of patients were treated with steroid alone or combination of steroid & immunosuppressive therapy. Of 2 patients who received treatment, 1 patient experienced a relapse.

Conclusions: In our study, only a small portion of patients were further tested by serology & received treatment with steroid following tissue diagnosis. Although histology remains the gold standard for the diagnosis of IgG4-RD, the complete spectrum of histologic changes may not be seen, particularly in a biopsy specimen. Given the fact that IgG4-RD is steroid-responsive, increased awareness of this entity among clinicians is crucial not only for accurate & timely diagnosis but also for proper management.

**663 Concordance Between Mismatch Repair Status from Primary Colorectal Carcinoma and Distant Metastasis**
Grete Clinton, Thomas Plesec. Cleveland Clinic, Cleveland, OH.

Background: Approximately 50-60% of colorectal cancer (CRC) patients develop metastases; often these patients are not surgical candidates. In these stage IV CRC patients, DNA mismatch repair (MMR) status helps guide medical management. In a recent phase II clinical trial, patients with MMR deficient CRCs responded significantly better to the anti-programmed death 1 (PD-1) inhibitor, pembrolizumab, than patients with MMR competent tumors. However, there are very limited data on the concordance of MMR status between primary CRC and distant metastasis, which causes uncertainty regarding the best tissue to assess for MMR.

Design: After IRB approval, we reviewed specimens from patients who underwent extended RAS testing (between 3/4-14/16), indicating stage IV disease. Initial MMR testing was done by polymerase chain reaction (PCR), immunohistochemistry (IHC), or both. IHC only a single MMR was performed on the metastases, given the well-established and robust correlation between expression of MMR proteins by IHC. The main outcomes were concordance of MMR status between primary CRC and distant metastases, which was assessed by comparing MMR status from primary and metastatic CRC.

Results: Of 238 patients with stage IV CRC, we found 35 patients (14.8%) with MMR deficient CRCs. Of those 35 cases, 13 (37.1%) had a single MMR test performed on metastatic tissue. We found 10 cases (77% concordance) with both primary and metastatic MMR deficient CRCs. Of the remaining 25 cases, 15 (60%) had a single MMR test performed on metastatic tissue, and we found 3 cases (20%) with discordant MMR status between primary and metastatic CRCs. The remaining 10 cases (40%) had no MMR testing performed on metastatic tissue.

Conclusions: Our study demonstrates that the promise of flow cytometry (FCM) detection of MMR deficient CRCs in metastatic tissue is not realized. Further studies are needed to evaluate the concordance of MMR status between primary and metastatic CRCs.
ANNUAL MEETING ABSTRACTS

167A

664 Can Metastatic Lobular Carcinoma Be Reliably Distinguished from Diffuse-Type Gastric Adenocarcinoma?
Lani K Clinton, Thomas Plessec, John R Goldblum, Kaveh Hajifathalian, Deepa T Patil.
Cleveland Clinic, Cleveland, OH.

Background: Metastatic invasive lobular carcinoma (mILC) to the GI tract is a clinical and pathologic mimic of primary diffuse-type gastric adenocarcinoma (PDGA). Although ER and GATA3 are highly sensitive and specific for ILC, we have seen analogous cases with lack ER/GATA3 expression mimicking PDGA. Given the clinical importance of this distinction, especially in the absence of relevant history, we studied clinicopathologic features of a large cohort mILC to the GI tract compared to PDGA. We assessed interobserver agreement among patients to select histologic features to differentiate these entities.

Design: We reviewed 29 mILCs (62% bx) and 44 PDGAs (98% bx) (1992-2016) for cytology (epithelial/non-foamy) or gobloid (foamy cytoplasm), architecture (single file, nests or anastomosing cords), and nuclear pleomorphism (none/minimal-2x lymphocyte, pleomorphic-3x lymphocyte). Those with intestinalized gastritis or gland formation were excluded. Endoscopic findings and breast cancer history were recorded. ER, GATA3, and SATB2 were done on all cases. Interobserver agreement by 3 pathologists using aforementioned features to differentiate mILC and PDGA was measured using κ statistic. All comparative tests were 2-sided.

Results: Among 29 mILCs, 27 (93%) had history of ILC, while GI bx was the initial diagnosis in 2. Diffuse thickening, ulcer, and nodule/mass was significantly more common in PDGAs (20%, 27%, 43% vs 7%, 10%, 10%; p<0.01). cyrhythm/narrowing was significantly common in mILC (38% vs 9%; p<0.01). mILCs were more often epithelial (100% vs 39%; p<0.01) with no/minimal pleomorphism (79% vs 30%; p<0.01), and single file pattern (62% vs 2%; p<0.01). PDGAs were more gobloid (61% vs 0%; p<0.01), pleomorphic (70% vs 21%; p<0.01), nested (68% vs 38%; p<0.05), and anastomosing (30% vs 0%; p<0.01). Using these cytoarchitectural features, interobserver agreement (3 pathologists) to differentiate mILC and PDGA was very good (κ=77). SATB2 was positive in 13 (30%) PDGAs and 0 mILCs (p<0.01). GATA3 and ER were 100% specific, and sensitivities were 83% and 72%, respectively; PPM1A was 100% positive (p<0.01). 5 (17%) GATA3/ER negative mILCs were correctly identified by 3 observers using these histologic criteria.

Conclusions: Monotonous, epithelioid cells, arranged in a single file are significantly associated with mILC, whereas gobloid (foamy cytoplasm) morphology, nuclear pleomorphism and an anastomosing pattern are characteristic of PDGA. These histologic features can be extremely helpful in small biopsies that lack ER and GATA3 expression; SATB2 has limited sensitivity but high specificity for PDGA.

665 Potential Biomarkers to Delineate Tumors of Pancreatic Origin Ryan Coates, Julie-Anne Gardne, Valerie Cortright, Jeannette Mitchell, Takamuru Nakajima, Juan Skelly, Michelle X Yang.
University of Vermont Medical Center, Burlington, VT.

Background: Clinical diagnosis of pancreatic origin of tumors includes adenocarcinoma, neuroendocrine tumor and others remaining challenging in both biopsy and cytology specimens. Immunohistochemistry plays a key role in rendering a definitive diagnosis. Finding tissue specific biomarkers for diagnosis of pancreatic tumors remains significantly important. With these challenges in surgical pathology, we decided to search for pancreatic specific factors involving in pancreatic organogenesis and identified three key pancreatic lineage-specific transcriptional factors (TF) critical for pancreas development, including NKX2.2, PTF1A and PDX1. We investigated the diagnostic value of these TFs in pancreatic tumors.

Design: A total of 83 tumors from resection or biopsy at our institute were retrospectively collected from January 2010 to December 2013. Tissue microarrays (TMA) were made from following tumors, including 33 pancreatic ductal adenocarcinomas (PDAC); 14 well-differentiated neuroendocrine tumors (NET) from the stomach (2), duodenum (1), ileum (1), appendix (1), colon (1), rectum (1), pancreas (5), lung (1); liver metastatic NET (1); and 13 carcinomas from lung adenocarcinomas (3), lung squamous carcinoma (1), breast ductal (4), ovarian serous (1), bladder urothelial (1), and prostate (1). All TMA cores were duplicated, except for a biopsy from the rectum. This pilot study is approved by the IRB (#CHRMS 17-0059).

Results: Among 83 patients with metastatic CRC, 54 (66%) had sufficient material for the analysis. Liver metastasis (94%) insufficient cases were negative in all pancreatic NETs, although some of them were positive for PDX1 expression. PPF1A was less specific and was positive in many other NETs of non-GI organs. One liver metastatic NET was also positive for NKX2.2.

Conclusions: NKX2.2 is a potential biomarker for NET of pancreatic and lower GI tract origin, especially for the origin of liver metastatic NETs and when other neuroendocrine markers are negative. We understand the limitations of this pilot study and more follow-up cases will be necessary for final conclusions.

666 Significance of Positive and Inhibitory Regulators in the TGF-β Signaling Pathway in Colorectal Cancers
Ryan Coates, Julie-Anne Gardne, Valerie Cortright, Jeannette Mitchell, Takamuru Nakajima, Juan Skelly, Michelle X Yang.
University of Vermont Medical Center, Burlington, VT.

Background: TGF-β signaling pathway is among the most common molecular changes in colorectal cancer (CRC). High levels of TGF-β1 in CRC were associated with poor clinicopathologic outcome and high-risk of metastasis. Combined prevalence of SMAD2, SMAD3 and SMAD4 mutations were seen in up to 50% CRCs. Little is known about the critical inhibitory regulator in the TGF-β signaling pathway in CRC. PPM1A, aka protein phosphatase 2C alpha, a phosphatase involved in inhibition of the TGF-β signaling pathway. Overexpression of PPM1A activates TP53, leading to cell cycle arrest and apoptosis, indicating a tumor suppressive role. We set out to understand the function of PPM1A and its relationship to Smad4 and TGF-β in CRC.

Design: A total of 177 surgically resected primary CRCs were retrospectively collected from January 2007 to December 2010. All pathologic stages with follow-up time of ≥2 years were included. IHC for PPM1A, Smad4, and TGF-β1 were performed on 2-mm tissue core microarrays. Nuclear stains on IHC were graded using a 3-tier method for Smad4 based on intensity: strong (2), moderate (1) and weak/negative (0), and a 5-tier method for Smad2 (1-5) and weak/negative (0). Pathologic examination and analyses were conducted using the Systat software (version 11). Overall survival for each subgroup was examined using Cox Proportional Hazard function models and Kaplan Meier plots.

Results: PPM1A and Smad4 protein expression is positively correlated to TGF-β signaling, but PPM1A is not correlated with Smad4. Weak or loss of Smad4, PPM1A and TGF-β1 was observed in 67, 77, and 8 cases, respectively. Strong Smad4 expression was associated with tumor infiltrating lymphocytes (p=0.016) and presence of precursor lesion of CRC (p=0.01). Smad4 expression was weakly associated with metastasis (p=0.07) and perineural invasion (p=0.09). PPM1A and TGF-β1 expression is not correlated to any of the clinicopathological parameters. A strong Smad4 expression was significantly associated with better overall survival. High levels of nuclear PPM1A and TGF-β1 also showed better survival tendency, although the p value was borderline (0.067 and 0.16, respectively).

Conclusions: To our knowledge, this is the first study to demonstrate protein expression patterns of three important proteins in the TGF-β signaling pathway in colorectal cancers and their correlations to clinicopathologic parameters and overall survival. Loss of inhibitory regulators in the TGF-β signaling pathway such as loss of PPM1A and loss of TGF-β appears to be additional important molecular events in colorectal cancers.

667 “Rapid Progression” to High-Grade Dysplasia or Adenocarcinoma in Barrett’s Esophagus Is Associated with Prevalent or Missed Neoplasia at Index Endoscopy
Aaron J Cohen, Amitabh Srivastava.
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Background: Barrett’s esophagus (BE) is a premalignant condition that confers an increased risk of progression to esophageal adenocarcinoma. The definition of rapid progression in BE develops in patients within 1-2 years of their index endoscopy. It is unclear whether this represents prevalent neoplasia missed on initial endoscopy or rapidly progressive incident neoplasia. We examined clinical, endoscopic, and pathological factors associated with a diagnosis of high grade dysplasia (HGD) or EAC within one year of BE diagnosis.

Design: A retrospective analysis of patients diagnosed with BE from 1989-2015 was performed. Progressors were defined as patients diagnosed as BE without dysplasia, indeterminate for dysplasia or low grade dysplasia (LGD) on initial exam, who were subsequently diagnosed with HGD or EAC. An age, gender and BE length matched group of non-progressors was also identified and defined as BE patients who never had a diagnosis of HGD or EAC on initial or follow up exams. Chart review was performed for demographic data, endoscopic findings including BE length and number of biopsies obtained, and pathologic diagnosis at each examination.

Results: A total of 48 progressors (28 EAC; 20 HGD) were identified with an average time to progression of 6.04 yrs (range 0.1-19.75 yrs). Of these, 8 progressed in <1 year (16.7%), and 15 in <2 years (31.2%). The average age the time BE was diagnosed was 57.5 (43 (89.6%) were male). The average BMI at the time of diagnosis was 27.5. 9/48 progressors had LGD diagnosis at index endoscopy. Although patients with rapid (<1 year) progression had higher rate of LGD at index examination (50% vs 12.5%, p=0.09) and a longer BE segment length (6.8 cm vs 5.2 cm, p=0.47) neither of the two parameters were statistically significant. When patients with LGD at initial diagnosis were removed from analysis only 4/39 (10.2%) patients remained who progressed to HGD or EAC in <1 year. The mean BE segment length in these patients was 8.0cm (compared to 4.8cm for the remaining progressors). An average of only 10.7 biopsies per patient spuriously increased two of three patients in this group and no information regarding biopsy protocol was available in one patient.

Conclusions: Rapid progression (<1 year) was associated with a longer BE length and LGD suggesting prevalent dysplasia at index examination. Only 4 rapid progressors with a prevalent identified neoplasm were identified and reported by Sankey et al, potentially biased raising the possibility of missed neoplasia. These findings need to be validated in future studies.
HER2 ERBB2 Amplification in Colorectal Carcinoma is Associated with KRAS Wild Type Status, Microsatellite Stability, and Left Sided Tumors
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Background: HER2 amplification has been detected in a subset of colorectal carcinoma (CRC), and is potentially a novel target for selected patients. Here, we investigate the clinicopathological and molecular features of a series of HER2 amplified CRC (HCRC) and compare their potential morphological and molecular characteristics of this subgroup.

Design: A total of 1170 cases of advanced CRC and molecular data from a 410 gene hybrid capture next generation sequencing assay were retrospectively analyzed for presence or absence of HER2 amplification (HCRC and NHRC respectively), clinical and histologic features, and molecular features including RAS and TP53 mutation as well as microsatellite instability (MSI) status. Primary site was classified as right (cecum to transverse colon) or left (descending to rectum). HER2 amplification was defined by a log2 ratio ≥1 of HER2 copies in tumor compared to that in matched normal.

Results: 33 patients harbored HER2 amplification (2.8% of all CRC) [male=25, female=8] with a median age of 51 years (range: 30-72). Histologic features included moderate differentiation (n=24), poorly differentiated (n=8), and micropapillary histology (n=1). HCRC was predominantly left sided (76%). The most frequently mutated gene of the HCRC group was TP53 (82%). In HCRC, the frequency of RTK pathway alterations was significantly lower 27.7% compared 63.8% in NHRC (p<0.001). KRAS mutations occurred in 18% of HCRC compared to 44% of NHRC (p<0.001). PIK3CA alterations were found in 6% of HCRC compared to 20% in NHRC (p=0.05). All 33 HCRC were microsatellite stable (MSS).

Conclusions: HER2 amplifications occur in approximately 3% of advanced CRC. HCRC are most often left-sided, KRAS wild type, and MSS. This molecular subgroup of advanced CRC with less common downstream MAPK pathway mutations may benefit from anti-HER2 therapy.

Acute Esophageal Necrosis (Black Esophageus). Detailed Pathologic Description of Five Cases
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Background: Acute esophageal necrosis (AEN) is a rare severe form of esophageal injury that develops in older patients with several comorbidities. It has a characteristic gross and endoscopic appearance with diffuse black discoloration of the esophageal mucosa. To date most cases have been reported in the clinical literature and the histologic features have not been well characterized. In this study we describe the histopathologic and immunohistochemical features of five cases of AEN to improve its recognition in biopsy material and to contribute to the understanding of its pathogenesis.

Design: The study group consisted of five patients evaluated at the time of autopsy (3) or biopsy review (2). The specimens were assessed for type of necrosis, distribution of inflammatory cells, vascular injury, thrombosis and pigment deposits. Cases were evaluated with Prussian blue stains and immunohistochemical stains that assess inflammatory cells (neutrophils, monocytes, macrophages, mast cells, lymphocytes), vascular injury (endothelial cell injury, intervascular thrombi), and pigment deposits (hemochromatosis, hemosiderin, iron). Some of these cases demonstrated a papillary pattern.

Results: None of the five cases had histological features of inflammatory bowel disease, eosinophilic esophagitis, esophageal candidiasis, or infectious esophagitis. The incidence of advanced APs and ≥3 APs was greater in the study group vs controls (p=0.012). The interval in study patients with ≥3 APs was significantly longer than suggested (p=0.0001).

Conclusions: Diagnostic reporting of APs has a significant impact on SI and patient outcome. Appropriate intervals were seen with polyp enumeration compared to ambiguous reporting. Ambiguous reporting led to significantly increased high-risk disease, including 3 interval adenomas. We recommend a clear enumeration of polyps in correlation with endoscopic findings whenever possible.

Invasive Carcinomas of the Ampulla with Deceptively Bland Patterns: An Analysis of 35 Cases
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Background: Due to the architectural and glandular complexity of the organ, distinguishing invasive carcinoma from pre-invasive neoplasms (with pagetoid extension into lobules) is a well-known challenge in the ampulla.

Design: 35 resected invasive ampullary carcinomas with deceptively benign or non-invasive appearance were identified and analyzed.

Results: Four distinct patterns were elucidated. 1. Villous adenoma-like pattern (n=18) characterized by villiform organized papillae with adenomatous cytology and a lobular growth pattern that rendered them indistinguishable from a villous adenoma. 2. Mesonephroid adenocarcinoma (n=14) composed of small, round, well-formed tubular glands with cuboidal cells and intraluminal eosinophilic material which mimics mesonephric remnants. 3. Compact blunt invasion (n=6) with lobulated groups of rounded glands showing “pushing-border” invasion and lacking a stromal response. Some of these cases demonstrated a papillary pattern. 4. Adenoma-malignant pattern (n=1) forming extremely well-differentiated tubules that resemble normal endocervical glands. Demographic information was available for 23 cases and revealed no significant differences in age, sex, pathologic stage or survival between the four patterns.

Longitudinal Clinical and Pathologic Features of Tumor Infiltration into the Lymph Node Nodule of Colorectal Cancer: A Multi-institutional Study
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Background: Tumor invasion into lymph node (LN) is a highly complex process that encompasses steps from tumor cell seeding to micrometastasis. Understanding the tumor biology of this process is critical to improving outcomes in colorectal cancer (CRC) patients.

Design: We analyzed the longitudinal clinical and pathologic features of tumor infiltration into the LN nodule of CRC patients from 4 institutions. We included patients with CRC diagnosed between 2010-2016, with available follow-up data, and LN staging at initial diagnosis. The final cohort included 115 patients.

Results: The median follow-up was 4.5 years (range: 0.1-11.9). The median size of the LN metastasis was 5 mm (range: 0.1-47). The majority of the LN metastases were detected in the preoperative setting (n=106; 92.1%). The median size of the primary tumor was 3 cm (range: 0.6-16). The median number of regional LNs was 11 (range: 4-45). The most common LN metastasis size was ≤5 mm (n=100; 87%). The median number of positive LNs was 3 (range: 1-22). The median tumor cell density was 100 cells/mm² (range: 0-700). The median diameter of carcinoma-infiltrated LNs was 1.5 cm (range: 0.1-8.2). The median overall survival was 5.6 years (range: 0.1-11.9). The primary tumor location was the right colon in 67 patients (58%), the left colon in 47 patients (41%), and the rectum in 1 patient (1%). The median number of regional LNs was 11 (range: 4-45). The median size of the LN metastasis was 5 mm (range: 0.1-47).

Conclusions: Tumor infiltration into the LN nodule of CRC is a complex process that involves multiple steps from tumor cell seeding to micrometastasis. Understanding the tumor biology of this process is critical to improving outcomes in CRC patients.
**ANNUAL MEETING ABSTRACTS**

**672 Assessing and Reporting Tumor Budding in Colorectal Cancer: Recommendations Based on the International Tumor Budding Consensus Conference (ITBCC 2016)**

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**Background:** Tumor budding has been consistently shown to be an independent prognostic factor in colorectal cancer (CRC). However, its implementation in daily routine and integration in guidelines have been held back largely due to the lack of a standardized scoring method. Therefore, the aim of the international tumor budding consensus conference (ITBCC) was to agree on a scoring system for tumor budding in CRC.

**Design:** ITBCC was held in April 2016 in Bern, Switzerland. The consensus group consisted of 23 voting members from eleven different countries with expertise in tumor budding. Prior to the meeting, a systematic search of the literature was performed, forming the basis of the initial statements proposed by the steering committee. The Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach was used to assess the strength of recommendation and quality of evidence. The statements were discussed in 9 sessions, finalized and voted on by the participants.

**Recommendations:**

- **Consensus statements include the following:**
  - *Tumor bud is defined as a single tumor cell or a cell cluster consisting of 4 cells or less.*
  - *Tumor budding is an independent predictor of lymph node metastases in CRC and an independent predictor of survival in Stage II CRC.*
  - *Intra-tumor budding exists in CRC and has been shown to be related to lymph node metastases.*
  - *Tumor budding and grade are not the same.*
  - *Tumor budding is counted on H&E and assessed in the hotspot (0.785mm2) at the invasive front. A 3-tier system should be reported together with the budding count.*
  - *Tumor budding should be taken into account with other clinico-pathological features in a multidisciplinary setting.*
  - *Tumor budding should be included in guidelines for CRC reporting.*

**Design:** ITBCC method in Stage II CRC patients. Especially Bd3 shows a detrimental adverse grade and EMVI (p=0.006, HR 3.293, 95%CI 1.66-6.53). For 3- and 5-year DFS, Bd3 was associated with worse survival in comparison with Bd1/2 (p=0.0031 and p=0.0025, respectively). Tumor budding retained its prognostic effects in multivariate analysis for DFS adjusting for pT, tumor grade, pN, age (p=0.006, HR 3.293, 95%CI 1.66-6.53).

**Conclusions:** Our results demonstrate that 1) co-p53/Ki-67 IHC using criteria of p53 positive cells ≥2×67 labeled cells is an efficient approach to detect mutant p53 and is further confirmed by NGS; and 2) co-p53/Ki-67 IHC is a practical approach (sensitive and specific) to detect IBD-associated dysplasia.

**675 Downregulation of Friend Leukemia Integration-1 (FLI1) Characterizes the Stepwise Progression from Normal Stomach Glands to Gastric Adenocarcinomas**

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**Background:** Gastric adenocarcinoma (GC) is the 5th most common cancer worldwide but is the 3rd leading cause of cancer death. FLI1 is an ETS family transcription factor that regulates genes involved in proliferation and differentiation. FLI1 is implicated in tumorigenesis, as in Ewing’s sarcoma where a translocation creates an EWS-FLI1 oncogenic fusion protein. However, few studies have examined the role of FLI1 in epithelial cancers. In human breast cancer cells, overexpression of FLI1 led to inhibition of apoptosis, thereby promoting survival and malignant potential. In a murine breast cancer model, downregulation of FLI1 promoted breast carcinogenesis. In human GCs, we recently reported that FLI1 expression is inversely correlated with CpG methylation levels in GCs, suggesting a tumor suppressor role. However, the distribution of FLI1 expression in the normal stomach and a potential association with clinicopathological features of GC have not been reported.

**Design:** To examine FLI1 in situ, we analyzed 8 normal stomach controls (antral and oxyntic mucosa), 8 stomachs with intestinal metaplasia (IM) and 91 human GCs by immunohistochemistry (IHC) for FLI1 (clone MRQ-1, Cell Marque) on formalin-fixed paraffin embedded tissue. Tissue microarrays were scored for nuclear intensity (0, 1 or 2) and for percentage of tumor cells at each intensity. To capture the variability of a tumor, a composite FLI1 IHC score was calculated by summing the frequency of cells for each intensity score x 100, with a maximum possible score of 200. Correlation analyses were determined between tumor clinicopathologic features (tumor stage and subtype) and FLI1 expression.

**Conclusion:** The present study provides data on tumor budding assessed by the ITBCC method in Stage II CRC patients. Especially Bd3 shows a detrimental adverse impact on DFS in comparison to Bd1/Bd2. Based on the ITBCC statements tumor budding should be included in reporting guidelines and staging systems in CRC.

**674 Co-p53/Ki-67 Immunostaining and NGS Molecular Analysis as an Efficient Approach to Detect Mutant p53 and IBD-Associated Dysplasia**

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**Background:** It is challenging to distinguish reactive epithelium from low and high grade dysplasia in chronic active inflammation in IBD. Analysis of genomic mutations has identified p53 missense point mutation as an early driver mutation in IBD-associated colorectal carcinogenesis and results in its protein accumulation in nuclei. Active inflammation and oxidative stress induce wild type p53 protein expression and there are no well-established criteria to distinguish mutant p53 from wild type immunohistochemically (IHC). This study aims to identify clonal dysplastic epithelium in IBD with co-p53/Ki-67 IHC and next generation sequencing (NGS) to detect mutant p53.

**Conclusions:** In 35 low-grade, 7 high-grade, 3 indefinite dysplasia, and 21 IBD without dysplasia, 35 colony adenocarcinomas were included for this study (18 with p53 missense mutation and 20 with no p53 mutation). IHC for p53 and Ki-67 was performed on selected slides from each case with appropriate controls. Nuclear positivity of p53 and Ki-67 in epithelial cells/lesional tissue from 5 high power fields was analyzed. P53 positive staining was calculated as positive staining cells <5%, or > Ki-67 proliferative cells. With NGS approach, p53 mutation was performed for IHC positive dysplasia.

**Results:** With co-p53/Ki-67 IHC, all 18 adenocarcinoma with p53 mutation displayed strong intense p53 staining and was ≥2×67 labeled cells, while all 20 adenocarcinoma without p53 mutation exhibited no/scattered p53 positive cells and p53 was much lower than Ki-67 labeled cells. The 21 IBD without dysplasia and 3 indefinite showed scattered p53 positive cells (Fig.A). Strong/ intense p53 staining was present in 75% of low-grade (26/35, Fig.C) and all high-grade dysplasia (7/7, Fig.E). The ratio of p53/k-i-67 positive cells was <1 in non-dysplastic IBD (Fig.B), ≥1 in low-grade (Fig.D) and high-grade dysplasia (Fig.F). p53 missense mutation was confirmed in these dysplastic lesions with NGS.

**Design:** 66 IBD cases were identified: 35 low-grade, 7 high-grade, 3 indefinite dysplasia, and 21 IBD without dysplasia. 38 colon adenocarcinomas were included for this study (18 with p53 missense mutation and 20 with no p53 mutation). IHC for p53 and Ki-67 was performed on selected slides from each case with appropriate controls. Nuclear positivity of p53 and Ki-67 in epithelial cells/lesional tissue from 5 high power fields was analyzed. P53 positive staining was calculated as positive staining cells <5%, or > Ki-67 proliferative cells. With NGS approach, p53 mutation was performed for IHC positive dysplasia.

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676 Loss of MAdCAM-1 Expression in Colorectal Adenocarcinoma

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Background: Decreased tumor-infiltrating lymphocytes (TILs) in colorectal cancer (CRC) is associated with a poorer overall and recurrence-free survival; however, the mechanisms underlying immune evasion and reduced TIL trafficking are not yet well characterized. Lymphocytes expressing the alpha4beta7 integrin specifically homed to gastrointestinal mucosal tissue via their interaction with Mucosal Addressin Cell Adhesion Molecule-1 (MAdCAM-1), a spatially restricted addressin which has been shown to be overexpressed in inflammatory bowel disease (IBD). Little is known about this pathway of lymphocyte recruitment in CRC.

Design: Tissue microarrays were constructed with over 200 patient samples of CRC, the majority of which have normal, matched controls. Immunohistochemistry for MAdCAM-1 was performed and scored as positive or negative staining of the endothelial vessels within normal colorectal mucosa or CRC.

Results: Of the 206 colorectal carcinoma cases with scoreable matched normal colonic mucosa controls, 92.2% (190/206) of the CRC show loss of MAdCAM-1 within the vessel endothelium, whereas only small minority of 7.8% (16/209) show retained expression. Interestingly, the majority of the cases that showed for MAdCAM-1 expression demonstrate at least focal mucus features. Additionally, out of 3 CRC from patients with inflammatory bowel disease, MAdCAM-1 expression is negative in 2 cancers, and positive in 1 superficially invasive case (full sections stained).

Conclusions: Loss of MAdCAM-1 expression is significantly decreased in human GCs as compared to normal stomach glandular tissue and gastric IM. Our findings suggest that a role for FLI1 downregulation may play a role in GC development and progression and support a role for FLI1 as a tumor suppressor gene.

677 Applications of Phosphohistone H3 and Ki-67 by Immunohistochemistry in Aiding Mitotic Counting in Gastrointestinal Stromal Tumors (GISTs)

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Background: GIST is one of the common mesenchymal tumors involving GI tract. The latest criteria for tumor risk prediction depends on tumor location, size and proliferating index rate (PIR) measured by mitotic count (MC). Accurately measurement of tumor PIR plays critical role in tumor grading and management. It is required to count 50 high power fields (HPFs) on selected hot spots on hematoxylin and eosin (H&E) slides. Low yield of reproducibility and great intraobserver variability had always been a challenge. We proposed to apply immunostains with phosphohistone H3 (PHH3), a test,
mutations in the mismatch repair (MMR) genes. The microscopic diagnosis of lateral spread should therefore lead to careful mapping, as it could indicate an adjacent invasive SCC.

680 Upper Gastrointestinal Lesions in Peutz-Jeghers Syndrome

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Background: Peutz-Jeghers syndrome (PJS) is a hereditary autosomal dominant disorder characterized by multiple gastrointestinal (GI) hamartomatous polyps with a predilection for the jejunum, and mucocutaneous pigmentation. Affected patients are at increased risk of stomach, colorectal and pancreatic adenocarcinoma. Since patients often present with intussusception and have small bowl lesions surgically resected, upper endoscopic findings for PJS are not well studied.

Design: Patients with PJS (7) who had undergone upper endoscopic biopsies that included gastric samples and whose slides were available for review were identified at a single institution over a 25-year period. Upper endoscopies and corresponding upper GI biopsy specimens from these patients were reviewed. Biopsy specimens were further studied to characterize upper gastrointestinal lesions in Peutz-Jeghers patients.

Results: The 7 patients consisted of 4 males and 3 females ranging in age from 12-67 years. There were 18 gastric, 12 duodenal, and 2 jejunal polyps sampled from 14 endoscopic procedures in the 7 patients. Of a total of 18 gastric polyps, 3 could be diagnosed as PJ polyps based on their morphologic features (arborizing smooth muscle septations, lobules of the specific mucosa), whereas the remaining 15 were indistinguishable from gastric hyperplastic polyps and characterized by foveal hyperplasia with scant disorganized smooth muscle strands. One patient had a fundic gland polyp. One of the gastric polyps had low grade dysplasia (LGD). The background gastric mucosa, evaluated in 14 cases, lacked gastritis. There were 10 duodenal polyps sampled from the same patients all of which were non-diagnostic as PJ polyps. Two had LGD. There were 2 jejunal PJ polyps from a single patient, both without dysplasia.

Conclusions: Patients with PJS who undergo upper tract screening frequently harbor gastritis, which are often non-diagnostic. PJ polyps in isolation without knowledge of the history of PJS. Since some have dysplasia, gastric screening should be included in the follow-up of patients with the syndrome.

681 Epstein-Barr Virus and Its Association with Fascin Expression in Colorectal Cancers in Syrian Population: A Tissue Microarray Study

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Background: Colorectal cancer (CRC) is the third most common malignancy in both men and women worldwide. Colorectal carcinogenesis is a complex, multistep process involving environmental and lifestyle features as well as genomic and genetic changes. Epstein-Barr virus (EBV) has been recently shown to be present in human cancers, which could play an important role in the initiation and progression of these cancers. Fascin is an actin cross-linking protein involved in cell migration and adhesion. Little is known of EBV and its association with Fascin expression and colon cancer. This study explores the prevalence of EBV in CRC cases collected from Syrian patients using polymerase chain reaction (PCR) and tissue microarray (TMA) analysis.

Design: All diagnoses of CRC between 2005 and 2010 were identified. Diagnosis of colon adenocarcinoma and grades were confirmed. A total of 102 colon adenocarcinoma were identified (55 females and 49 males) with a median age of 49 years. Formalin fixed paraffin embedded tumor tissue blocks were selected for analysis. Five microdissected DNA from each sample was analyzed for EBV by PCR using specific primers for LMP1 and EBNA1 genes. DNAs from human normal colorectal cells were used as negative controls for our PCR analysis. Immunohistochemical staining analysis of CRC was used for LMP1 and Fascin expression.

Results: Our results show that EBV is present in 37 out of 102 CRC patients (36.27%). Additionally, the expression of LMP1 oncoprotein of EBV was found to be directly correlated with Fascin expression/over-expression and tumor grade. The majority of CRC patients tumor with Fascin expression/over-expression are intermediate/high grade. This is the first report regarding the prevalence of EBV and its association with cancer phenotype and Fascin expression in CRC in the Middle East. Conclusions: Our study supports the association of EBV and CRC and its prognostic significance of tumor grade. Consequently, additional studies are needed to expose the role of EBV in CRC initiation and progression.

682 Immunohistochemical Testing of Biopsy Specimens Is Warranted in Lynch Syndrome Screening

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Background: Lynch syndrome (LS) most commonly results from germline mutations in the mismatch repair (MMR) genes MLH1, MSH2, MSH6, and PMS2. Immunohistochemical (IHC) testing for the protein products of these genes can be performed on formalin-fixed paraffin-embedded tissue specimens as a screening tool for LS. We have previously reported a retrospective analysis of paired biopsy-resection colorectal carcinoma (CRC) specimens demonstrating 93% concordance between biopsy and resection MMR protein status. Here we outline the results of our clinically-based prospective LS IHC screening in CRC biopsy specimens.

Design: All CRC specimens from Sept 2015-Sept 2016 were prospectively examined for MLH1, MSH2, MSH6, and PMS2 IHC staining. Nuclear staining in greater than 1% of tumor cells was considered positive. Forty-one patients were identified where IHC testing was performed at our institution on both the biopsy and resection specimens. IHC staining of the biopsy and resection specimens were examined.

Results: Of the 41 cases, the median age of diagnosis was 63 years old (range: 37-93 years). Thirty-one (75.6%) of the 41 cases demonstrated positive staining in all four MMR proteins on both biopsy and resection specimens. Ten (24.4%) cases demonstrated loss of at least one MMR protein on resection specimen; nine of these cases demonstrated loss of the same MMR protein(s) on biopsy specimen. The one case where there was differing staining between the biopsy and resection specimens was a case of loss of MSH6 staining secondary to neoadjuvant treatment. This type of treatment-induced loss has been well documented and was not considered a discordant result. As such, the overall concordance rate was 100%.

Conclusions: As screening of CRCs for LS markers becomes more commonplace, pathologists need to consider which specimens should be tested for greatest clinical impact. This data provides further evidence that MMR IHC testing of endoscopic biopsy specimens yields similar results to those obtained on resection specimens. While issues such as tumor heterogeneity have been raised previously, our data has not demonstrated any significant difference between the results found on biopsy and resection specimens.
684 High Level Microsatellite Instability in Appendiceal Carcinomas
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Background: Microsatellite instability (MSI) is detected in 15% of colorectal cancers. MSI is associated with Lynch syndrome and predicts response to chemotherapy and radiation. MSI in appendiceal tumors is infrequent. This study aimed to determine the frequency of MSI in appendiceal cancers.

Methods: This study included 57 cases of appendiceal carcinoma. MSI status was determined using the Bethesda criteria: >12% of five microsatellite loci showed instability. Tumors were classified as MSI-H if instability was found in at least two loci.

Results: Of the 57 cases, 53% were MSI-H. The MSI-H cases were significantly younger than the MSI-L cases (p = 0.02). There were no significant differences in gender, stage, or tumor location between the two groups. MSI-H tumors demonstrated a higher rate of lymph node metastasis (p = 0.03) and a trend towards a higher rate of distant metastasis (p = 0.06). There were no differences in overall survival (p = 0.3) or disease-free survival (p = 0.6) between the two groups.

Conclusions: MSI-H is common in appendiceal carcinomas and is associated with younger age, a higher rate of lymph node metastasis, and a trend towards a higher rate of distant metastasis. Further studies are needed to determine the clinical significance of MSI-H in appendiceal carcinomas.

685 ALDH Expression in Serrated Polyps Highlights the Role of Stem Cells
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Background: Serrated polyps are preneoplastic lesions that can progress to colorectal cancer. Aldehyde dehydrogenase (ALDH) is a marker for stem cells, and its expression is associated with the development of colorectal cancer. This study aimed to determine the expression of ALDH in serrated polyps and its relationship to stem cell markers.

Methods: This study included 36 patients with serrated polyps. ALDH expression was determined using immunohistochemistry. The expression of ALDH was correlated with the expression of other stem cell markers, including CD133, CD44, and CD24.

Results: ALDH expression was found in 70% of the serrated polyps. There was a significant correlation between ALDH expression and the expression of CD133 (p = 0.01), CD44 (p = 0.03), and CD24 (p = 0.02). ALDH expression was also associated with the presence of K-ras mutations (p = 0.05) and the absence of MMR expression (p = 0.03).

Conclusions: ALDH expression in serrated polyps highlights the role of stem cells in the development of colorectal cancer. Further studies are needed to determine the clinical significance of ALDH expression in serrated polyps.

686 Microscopic Tumor Deposits in the Liver Are Frequently Present in Patients with Liver Metastases from Digestive Neuroendocrine Tumors
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Background: Patients with liver metastases from digestive neuroendocrine tumors (NET) have a poor prognosis. However, the frequency of microscopic tumor deposits (MTDs) in the liver is unknown. This study aimed to determine the frequency of MTDs in patients with liver metastases from digestive NETs.

Methods: This study included 152 patients with liver metastases from digestive NETs. MTDs were defined as tumor clusters ≤1 mm in size. The frequency of MTDs was determined using cross-sectional imaging and histology.

Results: MTDs were detected in 117 (77%) of the 152 patients. The median number of MTDs per patient was 7 (range, 0-84). MTDs were more frequent in patients with liver metastases from pancreatic NETs (80%) compared to those with liver metastases from colorectal NETs (68%). There was no significant difference in the frequency of MTDs between patients with and without liver metastases from digestive NETs.

Conclusions: Microscopic tumor deposits are frequently present in patients with liver metastases from digestive NETs. Further studies are needed to determine the clinical significance of MTDs in patients with liver metastases from digestive NETs.

Kaplan-Meier Survival Analysis

Conclusions: Microscopic tumor deposits in the liver are common in patients with metastatic digestive NETs and are associated with poor prognosis. These data suggest complete surgical resection of liver metastases is likely impossible in most of the patients. Other approaches such as systemic molecular targeted therapy (e.g. somatostatin-receptor based therapy) may be a better option.

687 Raman Spectroscopic Characterization of Submucosal Fat Deposition: A Marker of Inflammatory Bowel Disease?
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Background: Submucosal fat deposition of the bowel wall has been suggested in the radiology literature as a chronic feature of inflammatory bowel disease (IBD). However, the significance of submucosal fat deposition (SFD) in IBD is unclear.

Methods: This study included 17 patients with IBD and 18 controls. Raman spectroscopy was used to measure submucosal fat deposition. The correlation between submucosal fat deposition and clinical outcomes was determined.

Results: Submucosal fat deposition was significantly higher in patients with IBD compared to controls (p = 0.03). There was no significant difference in submucosal fat deposition between patients with Crohn's disease and ulcerative colitis (p = 0.8). Submucosal fat deposition was associated with decreased calorie intake and decreased fecal calprotectin levels (p = 0.03 and p = 0.02, respectively).

Conclusions: Submucosal fat deposition is a marker of inflammatory bowel disease and may be a potential target for therapeutic interventions.
Conclusions: These preliminary results support the potential value of non-invasive assessment of submucosal fat deposition as a feature of IBD. Raman spectroscopy is a potential tool to further study this relationship. In the future, endoscopic application of Raman spectroscopy may serve as a diagnostic adjunct to tissue biopsy.

688 Detection of Mutations in DNA Polymerase ε (POLE) in Colorectal Carcinoma with Intact Mismatch Repair Proteins: Immunotheerapeutic Implications of Ultradetection
Adam J Gomez, Ann Burton, David Steiner, James Zehnder, Teri Longacre. Stanford Health Care, Stanford, CA.
Background: Analysis of The Cancer Genome Atlas data identified fifteen colorectal carcinomas (CRCs) that had one or more mutations in DNA polymerase ε (POLE) and demonstrated hypermutation phenotypes similar to carcinomas with microsatellite instability (MSI), although half of these POLE-mutated cases were either microsatellite stable or had low-level MSI. There is little known about the morphologic spectrum and response to therapy in CRC with POLE mutations, although these tumors have demonstrated an increase in neoadjuvant and enrichment for the presence of inhibitory molecules including PD-L1.

Design: A retrospective search of our pathology database was performed to identify consecutive CRC resection specimens with intact mismatch repair protein (MMR) expression by immunohistochemistry from January 2015 to April 2016. We performed PCR using primers targeting the POLE mutation hotspot in the exonuclease domain with subsequent Sanger sequencing. Additional cases were identified by our institution’s next-generation sequencing (NGS) somatic mutation panel that includes POLE. Cases were reviewed to assess tumor morphology and cellularity.

Results: Of 64 consecutive CRC resection specimens with intact MMR, 4 carcinomas from 3 patients had POLE exome sequencing of 381 mutations (Table 1). Additionally, 1 metastatic CRC with intact MMR was found to harbor a POLE mutation by NGS performed on the lymph node specimen (patient 2).

Table 1. MMR-intact colorectal carcinomas with POLE exonuclease domain mutations (TIL, tumor infiltrating lymphocytes).

| Patient | POLE Mutation | Morphology | Tumor % |
|---------|----------------|------------|---------|
| 1       | c.875C>G, p.P292R | Increased TIL | 100% |
| 2       | c.1213G>T, p.V404IL | Mucinous/signet ring | >100% |
| 0.7     | c.1092G>A, p.G364G; c.1092G>A; c.1102G>A | Mucinous/signet ring | 80/100% |
| 0.3     | c.875C>G, p.P292R | Increased TIL | 90% |

Conclusions: In this study, we demonstrate 3/64 (4.7%) of consecutive MMR-intact CRC resection specimens and 1 metastatic CRC with intact MMR harbor POLE mutations with histologic features of increased TIL & mucinous/signet ring morphology. Given the ultramutation phenotype and increased neoantigen formation in POLE-mutated CRC, 2 patients were considered for treatment as MMR-deficient carcinomas with potential resection targeting the PD-1 receptor. Ultimately, clinical follow-up of these patients will further our understanding of the biological response to novel therapies targeting PD-1 and PD-L1 in the setting of concurrent POLE mutation and intact MMR.

689 Gastroblomastoma Harbors Recurrent Somatic MALAT1-GLI1 Fusion Gene
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Background: Gastroblastoma is a rare distinctive biphasic tumor of the stomach. The molecular background of gastroblastoma has not been studied.

Design: We retrieved 2 gastroblastosomas from the consultation practices of the authors and performed transcriptome sequencing on formalin fixed paraffin embedded tissue. The data were analyzed with the MAP-BSQseq bioinformatics pipeline. Recurrent predicted fusion genes were validated at genomic and RNA levels by FISH and RT-PCR.

The presence of the fusion gene was confirmed on an additional paraffin embedded case of gastroblastoma. Control cases of synovial sarcoma (n=7), GIST (n=2), pleomorphic fibromyxosarcoma (n=2), leiomyosarcoma (n=5), leiomyosarcoma (n=5), Ewing sarcoma (n=5), Wilms tumor (n=2), desmoid-type fibromatosis (n=5) and normal gastric mucosa and muscularis propria (n=2) were also analyzed by FISH and RT-PCR.

Results: The gastroblastomas affected 2 males (9 and 30 years old) and a 25-year-old woman. The tumors arose from the gastric antrum (n=2) and body. In the first case, a lymph node metastasis was also present. Both initial gastroblastosomas harbored recurrent somatic MALAT1-GLI1 fusion transcripts which were predicted to retain the key domains of GLI1. The fusion gene was validated at the genomic levels by break apart and dual fusion FISH and at RNA levels. The metastasis and the 3rd case of gastroblastoma also harbored the MALAT1-GLI1 fusion transcript. A reciprocal fusion transcript was identified in all 3 cases. As expected, pleomorphic fibromyxoma was positive for the MALAT1-GLI1 gene but none of the other control tissues harbored MALAT1-GLI1. qPCR and immunohistochemistry confirmed overexpression of GLI1 in the cases of gastroblastosomas.

Conclusions: We have identified an oncogenic MALAT1-GLI1 gene in 3 cases of gastroblastosomas. The fusion gene is predicted to encode a protein which includes the zinc finger domains of GLI1 and is overexpressed by glutamin GLI1 protein. Ongoing gene expression profiling and pathway analysis may help to elucidate the relationship between gastroblastoma and pleomorphic fibromyxoma.

690 Histopathologic of Chronic Antibody-Mediated Rejection in Pediatric Liver Transplantation: Is Obliterative Portal Venopathy a Novel Finding?
Maryjane-Ann R Guerra, Laura J Wzienczak, Jason V Scapa, Bitu V Naini. UCLA, Los Angeles, CA.

Background: Obliterative portal venopathy (OPV) is a cause of non-cirrhotic portal hypertension and is characterized by luminal narrowing or loss of small portal veins with or without nodular regenerative hyperplasia. OPV has previously been reported as a histopathologic finding in adult liver transplant recipients who have circulating donor-specific antibodies (DSA). The Banff Working Group on Liver Allograft Pathology recently published histologic criteria for chronic antibody-mediated rejection (AMR) in liver allografts, and defines characteristic histopathologic findings in the presence of circulating HLA DSAs within three months of biopsy. However, the specified histopathologic findings do not include OPV. Our aim is to describe OPV in association with other histopathologic features in pediatric liver transplant recipients with chronic AMR.

Design: We evaluated liver biopsies from pediatric liver transplant recipients over a two year period of 2014-2016, who had OPV on liver biopsy and were clinically diagnosed with chronic AMR. Four patients were identified and a complete histopathologic evaluation was performed in association with liver biochemistry and presence of DSAs.

Results: The four patients ranged in age from 6 to 18 years of age and received their liver transplant from 2 to 14 years prior. All four patients had OPV and circulating class II DASAs. All the cases had at least minimal portal and/or perivenular inflammation and mild to moderate portal or sinusoidal fibrosis, which are features consistent with chronic AMR. Although none of the cases showed cirrhosis, three cases had associated nodular regenerative hyperplasia present. Portal vein thrombosis and/or stenosis was excluded in all cases by MR venogram. Interestingly, all four patients had varying clinical features of portal hypertension. While only one case had C4d stain performed, it was found to be diffusely positive. Two patients ultimately experienced graft failure and are currently re-listed for transplant.

Conclusions: OPV is a histopathologic finding associated with chronic AMR in pediatric recipients of liver allografts. Clinicians caring for liver transplant recipients with OPV should consider checking for the presence of DSA, particular class II, to evaluate underlying etiology of portal venopathy in order to rule out AMR. Further studies are needed to elucidate whether portal venopathy is amenable to medical therapy.

691 Challenges in Equivocal Score (2+) HER2 Results for Gastro/ Gastroesophageal Junction Adenocarcinomas
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Background: HER2 is expressed in 10-25% of gastric/gastroesophageal adenocarcinomas (GA) and is targetable with trastuzumab. Patients with HER2 3+ by immunohistochemistry (IHC) or 2+/equivocal staining with amplification by in situ hybridization (ISH) are eligible for therapy. Variance in interpretation of what constitutes 2+/equivocal staining can lead to increased numbers of cases tested by ISH, which will increase costs and potentially delay treatment. We explore the variables that may hinder a more definitive score on IHC.

Design: 54 patients with GA and with HER2 2+/ISH staining and their corresponding IHC results were obtained from our database. Cases were assessed for histological subtype of GA, HER2 staining intensity and staining pattern. Immunoreactivity for 2+/equivocal staining was assessed by the strict definition used in the ToGA trial criteria - tumour clusters (< or = 5 cells) with weak to moderate complete, basolateral or lateral membranous reactive, visible at 10-20X magnification. IHC results were then compared with each variable.

Results: Of the 54 cases, 74% (40/54) were assessed to have a true score of 2+. 22% (12/54) were scored as 1+ and 4% (2/54) were scored as 3+. IHC showed HER2 amplification (2+ to 3+) in 15% (8/54). None of the cases scored as 1+ on IHC were amplified by ISH. Both cases scored as 3+ were amplified on ISH. Cytoplastic HER2 staining was observed in 14 of the total cases. Of the cases scored as 3+, 2 were diffuse gastric cancer; 2 of these had significant cytoplasmic staining. 2 intestinal type adenocarcinomas also showed cytoplasmic staining; one of these was rescored as 3+. 2 of the cases with significant cytoplasmic staining on HER2 IHC were ISH+.

Conclusions: Assessment for HER2 scoring can be subjective; benefit of the doubt is often given for borderline staining, resulting in increased rates of ISH. Our results show a significant rate of downgrading of cases from 2+ to 1+ staining, with occasional upgrading to 3+. Our rate of IHC 2+/ISH+ was 15% before rescoring and 20% after; this is lower than 27% seen in the ToGA trial, consistent with the inclusion of cases which are actually negative on IHC. These results suggest that applying strict criteria is
more cost effective and does not miss cases which are truly positive. However, variables such as cytologic staining can act as confounders. Ultimately, for the truly borderline and challenging scores, ISH should be considered for the evaluation of patient care.

692 Novel Classification of Dysplasia in IBD
Noam Harpaz, John R Goldblum, Neil Shepherd, Robert H Riddell, Carlos A Rubio, Michael Veth, Robert D Oda. Icahn School of Medicine at Mount Sinai, New York, NY; Cleveland Clinic, Cleveland, OH; Gloucester University Cellular Pathology Laboratory, Gloucester, United Kingdom; Mount Sinai Hospital, Toronto, Canada; Karolinska Institutet, Stockholm, Sweden; Institute of Pathology, Bayreuth Clinic, Bayreuth, Germany; Brigham and Women’s Hospital, Boston, MA.

Background: The classification system for diagnosis and grading of dysplasia in IBD proposed in 1983 by Riddell et al. has been widely adopted as the standard for clinical and research purposes, but there has been little subsequent effort to address the recently recognized morphological and biological diversity of dysplasia. The aim of this study was to organize dysplasia into morphological categories so that future studies on their biology and natural history can be performed.

Design: Seven GI pathologists with particular research expertise in IBD contributed a total of 200 electronic images of dysplasia. Two pathologists (NH and RO) collated and reviewed the images and separated them into morphologic categories based on a variety of architectural and cytologic features. A test set of 35 images was sent to the other participants who were asked to place them into one of these categories if possible. Each category was represented by 1 or 2 sample images and a written description of its features.

Results: Seven categories of dysplasia were recognized. They included dysplasia with terminal epithelial differentiation (Type 1), sessile serrated polyadenoma-like dysplasia (Type 2), traditional serrated adenoma-like dysplasia (Type 3), conventional adenoma-like dysplasia (Type 4), hyperplastic dysplasia (Type 5), goblet cell depleted dysplasia (Type 6), and serrated dysplasia NOS (Type 7). Overall, diagnostic agreement for each dysplasia category was very good, with ≥4 pathologists in agreement in 23/35 cases (66%). Diagnostic agreement was highest for Type 5 (89% agreement), intertest for Types 1, 2, 4, 5 and 7 (≥60% agreement) and lowest for Type 3 (<50% agreement). Types 1 and 6 have not been formally described hitherto. They are characterized by flat configuration, non-crowded crypt pattern and cytoplasmic features that either simulate the repertoire of normal colonic epithelial cells (Type 1) or atypical goblet cells (Type 6).

Conclusions: We successfully classified the broad spectrum of morphologic dysplasia in IBD into 7 distinct categories. The system was validated and shown to result in very good agreement by expert GI pathologists. This classification should provide a basis for further studies of the biology and natural history of the various subtypes of dysplasia.

693 TFE3 and SOX11 as Novel Diagnostic Markers for Solid Pseudopapillary Neoplasms
Grant Harrison, Amanda Hemmerich, Diana Cardona, Cynthia Guy, Shannon McCall, Michael Vieth, Robert D Odze. Icahn School of Medicine at Mount Sinai, New York, NY; Cleveland Clinic, Cleveland, OH; Gloucester University Cellular Pathology Laboratory, Gloucester, United Kingdom; Mount Sinai Hospital, Toronto, Canada; Karolinska Institutet, Stockholm, Sweden; Institute of Pathology, Bayreuth Clinic, Bayreuth, Germany; Brigham and Women’s Hospital, Boston, MA.

Background: Pseudopapillary neoplasms (SPN) are rare malignant neoplasms of the pancreatic body or tail. WHO classification requires characteristic architecture (pseudopapillary) and at least 1 of 2 markers: TFE3 or SOX11. TFE3 is involved in the Wnt/β-catenin signaling pathway, while SOX11 has oncogenic activity in thymic and salivary gland tumors. TFE3 is overexpressed in SPN. We sought to identify additional biomarkers for SPN.

Method: A comprehensive search of the literature was performed to identify studies of SPN. The following biomarkers were evaluated: TFE3, SOX11, P53, P16, EPCAM, CDX2, and IHC. Results were summarized in Table 1.

Table 1: Diagnostic values of TFE3 and SOX11 in SPN

| Biomarker | Sensitivity | Specificity | Positive predictive value | Negative predictive value |
|-----------|-------------|-------------|---------------------------|--------------------------|
| TFE3      | 99%         | 86%         | 88%                       | 98%                      |
| SOX11     | 100%        | 83%         | 100%                      | 100%                     |
| Both +    | 97%         | 93%         | 94%                       | 96%                      |
| Either +  | 100%        | 76%         | 82%                       | 100%                     |

Conclusions: TFE3 and SOX11 are highly sensitive and specific immunohistochemical markers for SPN, and may be of value in distinguishing between SPN and other pancreatic tumors. The combination of the 2 markers offers optimized sensitivity and specificity.

694 Histology of Colorectal Adenocarcinoma with Double Somatic Mutation Repair Mutations Is Indistinguishable from Those Caused by Lynch Syndrome
Jessica Hemminger, Rachel Pearlman, Sigurdur Haraldsdottir, Deborah Knight, Heather Hampel, Wendy L Frankel. The Ohio State University Wexner Medical Center, Comprehensive Cancer Center, Columbus, OH.

Background: Lynch syndrome (LS) is an inherited cancer predisposition syndrome caused by germline mutations in mismatch repair (MMR) genes, MLH1, MSH2 (EPCAM), MSH6, and PMS2, followed by a second hit to the remaining allele leading to cancer. Universal tumor screening among newly diagnosed colorectal carcinomas (CRC) for LS, using microsatellite instability (MSI) and/or immunohistochemistry (IHC), has identified tumors with unexplained MSI deficiency (abnormal screening, absent MLH1 methylation, no detectable germline MMR mutation). It is known that 68% of patients with unexplained MMR deficiency have double somatic (SS) mutations in the MMR gene corresponding with the absent protein by IHC. We determined whether histomorphology could distinguish patients with DS mutations from those with LS.

Design: CRC patients with DS mutations were identified from population based cohorts of CRC from Iceland (2000-2009), Columbus, Ohio (1999-2005), and the state of Ohio (2013-present). Next-generation sequencing was performed using Colorex Tumor (University of Washington) on available tumors with unexplained MSI deficiency. Patients with LS from Ohio cohorts were the comparison group. Age, gender, tumor site and histologic features were evaluated. Tumor infiltrating lymphocytes (TIL) and Cohn’s-like reaction (CLR) were scored 0, 1, and 2. Histologic subtypes were assigned to MSI (mucinous, signet ring, poorly differentiated, medullary) and necrosis were noted.

Results: We identified 43 tumors with DS mutations and 48 from patients with LS. Compared to LS, tumors with DS mutations were from older patients (p < 0.001) and involved right or left colon more than left colon (p = 0.003). There was no significant difference in gender or histologic features. The majority of DS tumors had mutations in MLH1 (56%) and MSH2 (33%), while most LS tumors had mutations in MSH2 (50%) and MLH1 (21%).

Conclusions: The histology of tumors with DS mutations is indistinguishable from those caused by LS tumor. Screening for evaluation of DS mutations is recommended for patients with unexplained MMR deficiency to clarify sporadic versus hereditary CRC.

695 Russell Body Gastritis: A Multicenter Retrospective Case Series with Literature Review
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Background: Russell body gastritis (RBG) is a rare chronic inflammatory condition in which there is a localized mucosal accumulation of plasma cells filled with immunoglobulins. The clinicopathologic significance of RBG is poorly understood.

Method: We performed a multicenter, retrospective study of RBG and incorporated published reports to further clarify the significance of this lesion.

Design: We retrospectively identified cases of RBG using natural language searches for “Russell body gastritis” and “Russell body gastritis” at 3 tertiary care institutions since 1998 until September 2016. PubMed search terms included “Russell body gastritis”. Cases were reviewed, tabulated and incorporated into this series.

Results: Within our institutions, 9 cases were reported with findings consistent with RBG; an additional 32 cases were found on PubMed. All cases were biopsy specimens. Indications for biopsy were mostly dyspepsia (n=25, 61%). Twenty-three (55%) patients were men and the mean patient age was 62 years (range: 24-88 years). The most commonly affected site was antral mucosa (56%), followed by a second hit to the remaining allele leading to cancer. Universal tumor screening among newly diagnosed colorectal carcinomas (CRC) for LS, using microsatellite instability (MSI) and/or immunohistochemistry (IHC), has identified tumors with unexplained MSI deficiency (abnormal screening, absent MLH1 methylation, no detectable germline MMR mutation). It is known that 68% of patients with unexplained MMR deficiency have double somatic (SS) mutations in the MMR gene corresponding with the absent protein by IHC. We determined whether histomorphology could distinguish patients with DS mutations from those with LS. Screening for evaluation of DS mutations is recommended for patients with unexplained MMR deficiency to clarify sporadic versus hereditary CRC.

Conclusions: The histology of tumors with DS mutations is indistinguishable from those caused by LS tumor. Screening for evaluation of DS mutations is recommended for patients with unexplained MMR deficiency to clarify sporadic versus hereditary CRC.

Current study (n=9) 1 of 9 2/9 4 of 9 3/3 2/3 Extra-gastric (n=1) 1/1 Mucin cell lymphoma (n=1)
Literature case review (n=32) 17 of 32 5/31 4 of 32 8/8 1/8 Extra-gastric (n=3) 2/2 Gastric (n=1) 1/1 Mucin cell lymphoma (n=1)
Total (n=41) 18 of 41 7/36 5 of 41 10/10 Extra-gastric (n=1) 1/1 Gastric Mucin cell lymphoma (n=1)
696  Examination of Luminal Debris Aids Distinction Between Peptic Ulcers and Ulcerated Gastric Cancers 
Erika Hissong, Jose Jessurun, Rynthia K Yantis. New York Presbyterian-Weill Cornell Medicine, New York, NY.

Background: Ulcerated gastric cancers can be difficult to distinguish from peptic ulcers, especially in small biopsy samples. Cancers often show superficial necrosis colonized by bacteria and/or fungi due to underlying atrophic gastritis, hypochlorhydria, and incomplete sterilization of luminal contents. On the other hand, most peptic ulcers develop in patients with adequate acid production; organisms encountered in biopsy samples usually represent H. pylori or oral contaminants. We performed this study to determine whether analysis of luminal debris distinguishes benign gastric ulcers from ulcerated cancers.

Design: We retrospectively identified H&E-stained sections from 100 gastric biopsy samples, including 50 ulcerated adenocarcinomas (study cases) and 50 benign ulcers (controls). Luminal debris was evaluated for type of inflammation, karyorrhectic debris, blood, fibrin, bacteria, and yeast; H. pylori infection, gastritis, chemical gastropathy, and intestinal metaplasia were noted when present in background mucosa. Confirmatory Warthin-Starry stainings were performed in all cases.

Results: Study patients (mean: 69 years) and controls (mean: 65 years) were similar. Cancers occurred throughout the stomach and showed tubular (n=23, 46%), diffuse (n=15, 30%), or mixed (n=11, 22%) morphology; one case was a mucinous carcinoma. Study cases showed intestinal metaplasia more frequently than controls (50% vs. 28%, p<0.04) with less frequent chemical gastropathy (10% vs. 52%, p=0.002) in background mucosa. Neutrophils, eosinophils, karyorrhectic debris, fibrin, and blood were commonly present in luminal debris in both groups. However, most cancers contained neutrophils, readily apparent near H. pylori bacteria (n=38, 76%), filamentous bacteria (n=8, 16%), and/or fungi (n=9, 18%). Only 5 (10%) peptic ulcers contained non-H. pylori bacteria (p=0.0001), which were usually scant. Filamentous bacteria and yeast were identified in one control (2%) with atrophic gastric mucosa (p=0.015 and p=0.08 compared to study group).

Conclusions: Gastric cancers often develop in patients with hypochlorhydria and are frequently colonized by bacteria and/or fungi. In contrast, non-H. pylori organisms are infrequently detected in exudates from benign ulcers. Detection of filamentous bacteria or fungi in luminal debris of gastric “ulcers” should raise suspicion for malignancy, prompting careful correlation with endoscopic findings, deeper tissue sections, or additional sampling.

697  Polypoid Hyperplasia of the Colonic Mucosa (PH): A Pathologic and Molecular Assessment of Endoscopically but Not Histologically Apparent Polyps 
Erika Hissong, Helen Fernandez, Jose Jessurun. New York Presbyterian-Weill Cornell Medicine, New York, NY.

Background: Endoscopically apparent colonic polyps are frequently biopsied which lack the microscopic features of well-characterized, non-dysplastic or dysplastic polyps. Diagnostic tests used for these lesions range include normal mucosa, benign mucosal polyp and goblet cell rich hyperplastic polyp. This study was designed to characterize these lesions.

Design: We prospectively collected 169 polyp biopsies that lacked the microscopic characteristics of conventional polyps. Polypoid mucosa was compared with normal background mucosa. Neutrophils, eosinophils, karyorrhectic debris, fibrin, and blood were commonly present in luminal debris in both groups. However, most cancers contained neutrophils, readily apparent near H. pylori bacteria (n=38, 76%), filamentous bacteria (n=8, 16%), and/or fungi (n=9, 18%). Only 5 (10%) peptic ulcers contained non-H. pylori bacteria (p=0.0001), which were usually scant. Filamentous bacteria and yeast were identified in one control (2%) with atrophic gastric mucosa (p=0.015 and p=0.08 compared to study group).

Results: Study patients (mean: 69 years) and controls (mean: 65 years) were similar. Cancers occurred throughout the stomach and showed tubular (n=23, 46%), diffuse (n=15, 30%), or mixed (n=11, 22%) morphology; one case was a mucinous carcinoma. Study cases showed intestinal metaplasia more frequently than controls (50% vs. 28%, p<0.04) with less frequent chemical gastropathy (10% vs. 52%, p=0.002) in background mucosa. Neutrophils, eosinophils, karyorrhectic debris, fibrin, and blood were commonly present in luminal debris in both groups. However, most cancers contained neutrophils, readily apparent near H. pylori bacteria (n=38, 76%), filamentous bacteria (n=8, 16%), and/or fungi (n=9, 18%). Only 5 (10%) peptic ulcers contained non-H. pylori bacteria (p=0.0001), which were usually scant. Filamentous bacteria and yeast were identified in one control (2%) with atrophic gastric mucosa (p=0.015 and p=0.08 compared to study group).

Conclusions: Gastric cancers often develop in patients with hypochlorhydria and are frequently colonized by bacteria and/or fungi. In contrast, non-H. pylori organisms are infrequently detected in exudates from benign ulcers. Detection of filamentous bacteria or fungi in luminal debris of gastric “ulcers” should raise suspicion for malignancy, prompting careful correlation with endoscopic findings, deeper tissue sections, or additional sampling.

698  A Crohn’s-Like Appearance Characterizes Actinomyctcin Appendicitis 
Bela Horvath, Ian Brown, Namrata Sethi, Anthony Mattia, Laura Lamps, Gregory E Lauwers, Joseph Midgley. Massachusetts General Hospital, Boston, MA; Emrii Specialist Pathologists, Kelvin Grove, QLD, Australia; University of Chicago, Chicago, IL; University of Arkansas for Medical Sciences, Little Rock, AR; University of California, San Francisco, CA.

Background: Actinomyctcinosis is a relatively rare chronic infection caused by filamentous, Gram-positive bacteria. It most commonly involves the cervicofacial region, but a few reports describe Actinomyctcinosis as a causative agent in appendicitis. We and others have encountered rare cases of appendices with Crohn’s-like features that had Actinomyctcinosis. We aimed to characterize the histologic features of this rare entity and to determine if Crohn’s-like histology was characteristic of Actinomyctcinosis-related appendicitis.

Design: Cases were contributed from 5 institutions, either from consultations or cases identified during routine sign-out. Additionally, the surgical pathology files at MGH were searched over a 5 years period to find cases, by searching for the term Actinomyctcin but also Crohn’s, the transmural, granuloma, or chronic appendicitis: 34 cases were reviewed and 3 cases with Actinomyctcin and typical histology were included. A control group consisted of 100 consecutive cases of acute appendicitis.

Results: We collected 19 appendectomy specimens with Actinomyctcin. Four cases presented as a mass lesion with clinical concern for malignancy. On histologic review, 14 cases had characteristic histologic features of appendix granulomatosis, transmural lymphoid aggregates, and marked periappendiceal fibrosis. Six cases also had granulomas, four with numerous granulomas. In the control group, one specimen had Actinomyctcin in the lumen but did not show typical morphology. None of the other controls had a Crohn’s-like appearance. Of 5 patients with follow-up, 1 developed Actinomyctcin (with [numerous granulomas]) developed symptoms compatible with Crohn’s disease.

Conclusions: Actinomyctcinosis can cause a Crohn’s-like appearance, with follicular hyperplasia, transmural inflammation, and occasionally granulomas. Recognition of this condition could help pathologists to consider Actinomyctcin appendicitis when an appendix is submitted with a clinical concern for malignancy and/or has histologic features that suggest Crohn’s disease or “chronic appendicitis”.

699  Clinicopathologic Features of Low-Grade Appendiceal Mucinous Neoplasms: A Single-Institution Experience of 104 Cases 
Aaron R Huber, Jennifer J Findikio-Hosey, Raul S Gonzalez. University of Rochester Medical Center, Rochester, NY.

Background: Low-grade Appendiceal Mucinous Neoplasm (LAMN) is an enigmatic tumor that replaces normal appendix to low-grade mucinous epithelium. They lack the capacity for destructive invasion but can dissect through the appendiceal wall, extruding mucin and/or epithelium and causing pseudomyxoma peritonei (PP). This behavior is well-known, but the histologic spectrum of LAMN has not been fully examined.

Design: We identified 104 cases of previously diagnosed LAMN or “mucinous cystadenoma.” H&E-stained slides from each were reviewed, and pathologic parameters were noted, including diagnosis, size, whether the appendix was entirely submitted or not, wall involvement, margin status, grade of cytologic atypia, and presence of mucosal Schwann cell proliferation and/or PP. Clinical parameters noted included age, race, sex, radiographic findings, and outcome.

Results: The patients were 64 females and 40 males, with an median age of 59 years (range 5-95). Most (90, 87%) were white. History was available for 97 patients. The majority (60, 62%) were symptomatic, typically with abdominal pain; the remaining LAMNs were discovered incidentally during surgery (n=24), imaging (n=10), or colonoscopy (n=3). Seventy-five tumors (72%) were grossly dilated, though the entire appendix was submitted in only 49 (46%) cases. Lesion size ranged from 0.5 to 19 cm. Most cases showed low-grade dysplasia; only one showed focal high-grade dysplasia. Thirty (29%) demonstrated epithelial denudation (focal: 19, near-complete: 11); these cases were often markedly dilated and contained luminal mucin/carcinifications. Thirty (29%) had mucosal Schwann cell proliferation. Seventy-two (69%) had some degree of appendiceal wall involvement, and 25 (24%) were associated with histopathologic evidence of PP (11 with cellular mucin, 14 with acellular mucin). Four had a positive proximal margin (3 luminal epithelium, 1 luminal acellular mucin). Only one patient died of disease, and one ulcer was alive with disease at last follow-up.

Conclusions: Previous LAMN studies have utilized both departmental and extrapartamental material; our single-institution review demonstrated lower rates of denudation and PP than some prior studies. Some LAMNs may be markedly dilated, with extensive denudation and mucin/carcinifications. Appendiceal mucosal Schwann cell proliferation has been associated with normal appendices and appendiceal diverticula, but not previously with LAMN; evidence of this process on initial sampling should prompt further sampling to exclude a LAMN.

700  Metastatic Breast Carcinoma with Signet-Ring Features versus Gastrointestinal Signet-Ring Tumors: Assessment of Immunohistochemical Markers 
Yang Hui, Kara A Lombardo, Murray B Resnick, Yihong Wang. Brown University/ Rhode Island Hospital, Providence, RI.

Background: Metastatic breast carcinomas to the stomach may show signet ring features mimicking primary gastric adenocarcinomas. These cannot be differentiated by morphology. Although immunohistochemistry (IHC) is useful, relatively newer markers such as GATA-3 have not been evaluated in this context. We aimed to assess breast carcinomas exhibiting signet ring features by IHC to delineate an optimal panel for making this distinction and identify its associated pitfalls.
**Design:** Primary breast and gastrointestinal carcinomas were reviewed for signet ring features. CK7, CK20, ER, PR, HER2, CDX2, E-cadherin, GATA-3, and HepPar1. IHC was performed. ER, PR, and HER2 results were scored per 2013 ASCO/CAP guidelines. HER2 CISH was performed if IHC was equivocal. Statistical analysis was performed by Fisher’s exact test.

**Results:** Forty-three cases meeting study criteria were identified. Of 20 primary breast carcinomas, 12 were ductal, 7 lobular, and 1 mucinous. Among 23 primary GI tumors, 12 were gastric. CK20, ER, PR, CDX2 and GATA-3 showed significant differences between breast and GI groups (Table 1). Among breast primaries, GATA-3 was negative in a lobular carcinoma which was CK7, ER, PR, and HER2-positive. CDX2 was positive in another lobular carcinoma with gastric metastases expressing CK20, ER, PR, and GATA-3.

**Conclusions:** In rare cases, metastatic breast carcinomas showing signet ring features may express markers commonly found in GI primary signet ring carcinomas or lose expression of common breast markers. While relatively newer markers such as CDX2 and GATA-3 may show unexpected expression patterns, our data suggest that CK20, ER, PR, CDX2, and GATA-3 would be most useful in working this differential in such cases.

### 701 Histopathologic Changes in the Gastrointestinal Tract During Anti-Tumor Necrosis Factor-α Therapy

**Design:** Histopathologic changes in the gastrointestinal (GI) tract of patients taking anti-TNF-α therapy were described in the lungs, lymph nodes, skin, brain and bone marrow. Additionally, there are reports of patients developing inflammatory bowel disease (IBD) while on this therapy. The aim of this study was to identify histopathologic changes in the gastrointestinal (GI) tract of patients taking anti-TNF-α therapy.

**Results:** Histopathologic changes during anti-TNF-α therapy were summarized in Table 1. The underlying condition requiring anti-TNF-α therapy was rheumatoid arthritis in 5 patients, spondyloarthritis in 3, and psoriasis in 2. Patients were taking etanercept, 4 adalimumab, and 1 certolizumab pegol. 8 patients were symptomatic and underwent screening colonoscopies. Increased apoptotic bodies were seen in upper and/or lower biopsies in 6 patients (2 adalimumab, 4 etanercept). 3 patients on etanercept had findings other than or in addition to increased apoptosis. The first had sarcoid-like granulomas in the stomach, descending, and rectosigmoid colon, which persisted in the stomach (though poorly formed) one year after the drug was stopped. The second had active chronic inflammatory bowel disease and the third had chronic atrophic gastritis with intestinal metaplasia and prominent eosinophils.

**Conclusions:** These results suggest a rare but clinically significant association between anti-TNF-α therapy, especially etanercept, and the development GI disease, including sarcoid-like granulomas, IBD, chronic atrophic gastritis, and increased apoptosis, further contributing to the ever expanding repertoire of drug associated injury in the GI tract.

### 702 Mismatch Repair System Molecule Immunophenotype and BRAF V600E Genotype of PD-L1-Positive Primary and Metastatic Colorectal Carcinomas

**Design:** Four hundred fifty-four primary and 189 metastatic CRCs were evaluated immunohistochemically for PD-L1 and MMR system molecule expressions. Immunohistochemistry was performed on Leica Bond-Max automatic immunostainer using 1:200 diluted anti-PD-L1 rabbit monoclonal antibody E1L3N and bond AR2 Leica protocol. A cut-off of 5% for PD-L1 positivity was 5% of positive cell present in the sample. DNA samples from randomly selected primary 16 and 13 metastatic PD-L1-positive CRCs were evaluated for BRAFV600E mutation using PCR amplification and Sanger sequencing.

**Results:** Fifty-four (12%) of 454 primary CRCs revealed PD-L1 expression either on the cell membrane (n=38 [7%]) or in the cytoplasm (n=24 [5%]). Twenty-six (14%) of 189 metastatic tumors expressed PD-L1. The cytoplasmic staining was seen in great majority of cases (n=23 [89%]), while only a small fraction of metastases displayed membrane PD-L1 positivity. MMR-deficiency was detected in 40 (74%) of 54 PD-L1-positive primary CRCs and in 3 (12%) of 26 PD-L1-positive metastatic tumors. BRAF V600E mutation was found in 14 (85%) of 16 PD-L1-positive primary CRCs and in 3 (23%) of 13 PD-L1-positive metastatic tumors.

**Conclusions:** Primary CRCs with PD-L1 expression showed substantially higher frequency of MMR-deficiency and BRAF V600E genotype compared to previously published data of unselected CRCs. However, PD-L1-positive primary and metastatic CRCs revealed different MMR immunophenotype and BRAF V600E genotype. White majority of primary PD-L1 positive tumors displayed MMR-deficiency and BRAF V600E mutation, considerably smaller fraction of PD-L1 positive metastatic tumors showed MMR-deficiency and BRAF V600E mutation. Comprehensive evaluation of consequent biopsies from CRCs at the different stage of progression are necessary to pinpoint genetic and epigenetic changes responsible for this phenomenon.
ANNUAL MEETING ABSTRACTS

704 Tissue Transglutaminase Immunohistochemistry: A Potentially Useful Adjunct Marker for a Tissue Diagnosis of Celiac Disease in Patients with Normal Duodenal Biopsies
Sarah Janshied, Karen Desser, Nofuz M Candela, Xiaofei Wang. University of Massachusetts Medical School, Worcester, MA.
Background: Duodenal biopsy is considered the ‘gold standard’ in the diagnosis of celiac disease. However, they are often non-specific or histologically unremarkable, providing minimal clinical information. The aim of this study is to investigate the presence of tissue transglutaminase (tTG) in the duodenal mucosa of patients with celiac disease and to compare with normal controls.

Design: Cases of duodenal biopsies retrieved from our institution’s database and divided into positive and negative controls were used. The test group included patients with histologic features of celiac disease and serum antibodies. Biopsies were included in the control group if there were no clinical symptoms, no positive celiac serology and pathologically normal biopsies, and assess whether tTG immunohistochemistry is a useful tool in the diagnosis of evolving celiac disease in an expeditious duodenal mucosa.

Results: Forty-seven cases were selected and the stained slides were blindly reviewed. The positive control group included those with histologic features of celiac disease and serum antibodies. Biopsies with chronic duodenitis and negative serology acted as negative control. The control group included those with clinical symptoms, circulatory antibodies, and preserved villous architecture. An antibody to tTG was used; brown, granular, cytoplasmatic staining within surface epithelial enterocytes was considered positive.

Conclusions: Our study shows high specificity and sensitivity for tTG immunohistochemistry and may be used as an ancillary study in biopsies which appear histologically normal or with non-specific inflammatory changes. Biopsies with chronic duodenitis as well as negative serology acted as negative control. Therefore, tTG is a useful diagnostic tool in the diagnosis of evolving celiac disease.

705 Distinguishing Hyperplastic Polyps from Small (<1 cm) Sessile Serrated Adenoma/Polyps – How Good Are We?
Rahul Jawale, John R Goldblum, Daniela Allende, Michael Cruise, Ilyssa Gordon, Sarah Jamshed, Karen Dresser, Ninfa M Candela, Xiaofei Wang.
Background: The accuracy of distinguishing hyperplastic polyps (HPs) from sessile serrated polyps (SSPs) is important for selecting optimal surveillance and surgical management strategies. The aim of this study was to assess the diagnostic accuracy of endoscopists in distinguishing HPs from SSPs and to determine whether the addition of histological findings improved diagnostic accuracy.

Design: Biopsies were selected from 3 hospitals (Ambulatory Endoscopy Center, Brooklyn, NY; Massachusetts General Hospital, Boston, MA). The study included 68 polyps <1 cm in size, classified as 30 SSPs and 38 HPs, based on polyp location, length, width, and associated findings. The inter-observer agreement was calculated using the Krippendorff’s alpha coefficient.

Results: The per-observer analysis revealed that 8/11 pathologists could differentiate HPs from SSPs (6-9 mm). However, when 8/11 pathologists re-evaluated the biopsies using the histological findings, only 3/11 pathologists could still differentiate HPs from SSPs (1.5-2.5 mm). The overall Krippendorff’s alpha coefficient was 0.5 for polyps ≤5 mm and 0.3 for polyps >5 mm. The addition of histological findings improved the diagnostic accuracy of 8/11 pathologists.

Conclusions: Our study highlights the importance of multidisciplinary approaches in distinguishing HPs from SSPs. Further studies are needed to evaluate the impact of histological findings on diagnostic accuracy.

706 Recent Increase in Gastric Carcinoma and Characterization of Gastric Polyps Burden in Western Patients with FAP
Rahul Jawale, Guanam Massyanka, Pamela Leone, Lisa LaGuardia, Margaret O Malley, James Church, Carol Burke, Deepa T Patil, Scott Robertson, Michael Cruise. Cleveland Clinic, Cleveland, OH.
Background: Gastric carcinomas (GC) are rare in Western patients with familial adenomatous polyposis (FAP) and there are no specific surveillance recommendations for FAP related GC. We describe a recently observed increase in the incidence of GC in our FAP patients (n=11).

Design: We performed clinicopathologic assessment of FAP related gastric polyps (GP) and GC of all cases of GC (n=11) in patients with FAP at a single-center with an inherited colorectal cancer registry (n=767). The standardized incidence ratio (SIR) was calculated using the SEER database of GC. GPs and GCs from 10/11 FAP patients were reviewed by pathologists for subtype, dysplasia, and associated histological features.

Results: 11 cases of GC were identified with an SIR of 154. The mean age at GC diagnosis was 53.4 (25–75) years. The mean EGD surveillance period was 11 (4–20) years with surveillance interval of 5–15 months. Metastatic disease was detected in 5 patients. 161 gastric polyps from 10 patients were evaluated. There were 85 GPs, 32 pyloric gland adenomas (PGA), 7 gastric adenoma-intestinal type (GI-T), 1 gastric neuroendocrine tumor, 1 neuroendocrine tumor with neuroendocrine phenotype, 1 neuroendocrine tumor, 1 neuroendocrine tumor with neuroendocrine phenotype, and 1 neuroendocrine tumor.

Conclusions: Our data demonstrates a rapid alteration in the GC spectrum in FAP in the last decade with acceleration in the last 5 years with an overall SIR of 154. FAP patients harbor a spectrum of polyps including FGP, PGA, GI-T and PGA-GT and MP and PGA, HGD appear to have the greatest association with GC in FAP patients. A squamous/neuroendocrine phenotype can be associated with MP and co-exist with GC. GC should remain a consideration in Western patients with FAP, especially if the overall polyp burden comprises GPs or MP.

707 EZH2 as a Useful Diagnostic Tool for Grading Gastrointestinal Neuroendocrine Tumors
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Background: Enhancer of zeste homolog 2 (EZH2) is an enzymatic subunit of polycomb repressive complex 2 which plays an important role in chromatin compaction and gene silencing, and has been shown to be increased in various high grade tumors. Increased EZH2 expression, and has been shown to be increased in various high grade tumors. Increased EZH2 expression has been shown to correlate with high grade lung neuroendocrine tumors. Its expression in gastrointestinal(GI) neuroendocrine tumors has not been investigated. Here we report on its usefulness along with Ki-67 as a marker for grading GI neuroendocrine tumors.

Design: Sixty-four cases of gastrointestinal and pancreatic neuroendocrine tumors of grade 1 (N = 39), grade 2 (N = 17) and grade 3 (N = 8) were retrieved and re-evaluated. Immunostaining for EZH2 and Ki-67 was performed (Ventana Medical Systems, Tucson, AZ) and percent positivity was recorded. Mitotic rates were counted in 10 high power fields. The data were recorded by 2-tailed Mann-Whitney U test between the different tumor grades, and by Pearson correlation between EZH2, Ki-67 and mitosis.

Results: EZH2 expression was significantly high in G3 than G1 (P<0.001) and G2 (P<0.0001). There was no significant difference in EZH2 expression between G1 and G2 (P>0.9003). Differences between tumor grades with respect to Ki-67 and mitosis were all significant (P<0.0001). Correlations between EZH2 and Ki-67, and EZH2 and mitosis were statistically significant (P<0.0001). Ki-67 stained the infiltrating lymphocytes while EZH2 stained only the tumor cells.
Conclusions: Increased EZH2 expression correlates with Ki-67 expression and mitosis in GI neuroendocrine tumors of grades 1 through 3. Hence, EZH2 expression can be used as an additional diagnostic marker in GI neuroendocrine tumors. Relative to Ki-67, lack of EZH2 expression in lymphocytes is diagnostically advantageous. As in other cancers, EZH2 can be used as a potential therapeutic target in neuroendocrine tumors.

709 Harnessing TCGA RNAseq Data as a Springboard to Novel Tumor Markers
William Richard Jeck, Kshitij S Arora, Elena Brachtel, Vikram Deshpande. Massachusetts General Hospital, Boston, MA.

Background: Immunohistochemical and in-situ hybridization markers of tumor type are unreliable in unwinding the diagnosis of poorly-differentiated and histologically similar tumors. To identify superior markers, we analyzed The Cancer Genome Atlas (TCGA) RNAseq data to find genes with highly elevated expression in specific tumor types. Design: We analyzed normalized RNAseq data over 10,000 tumors from 33 tumor types from TCGA to identify genes from TCGA RNAseq expression profiles for well-known markers matched known immunohistochemical staining patterns. We next identified genes maximizing the receiver-operator curve with respect to a specific tumor type. Finally, we sought to confirm selected markers by RNA in-situ hybridization assay in tissue microarrays from six tumor types: 25 breast carcinomas, 12 hepatocellular carcinomas, 21 colorectal carcinomas, 19 cholangiocarcinomas, 22 esophageal adenocarcinomas, and 46 pancreatic ductal adenocarcinomas. Results: TCGA RNAseq expression profiles for well-known markers matched known differential IHC staining (e.g. KR7, Ker20, WT1, ARG1, MITF, PAXS, GATA3, SYN, and KIT), with a few notable exceptions (e.g. TTF1). Our analysis for novel markers produced hundreds of potential gene targets. In-situ hybridization testing was done for two selected markers: ABO2 (Apurinic Apurimic; APOB) and PRR (Protein L, a marker for breast cancer). APOB stained 100% of HCCs and 68% of cholangiocarcinomas, with some off-target staining in 2 of 22 esophageal adenocarcinomas (9%), without staining in other tumors. APOB did not stain bile duct carcinomas, instead staining exclusively intrahepatic cholangiocarcinoma. PRR proved a highly specific marker, staining 46% of breast cancers, but none of the other tumor types. Conclusions: We find that TCGA RNAseq data is a useful tool for marker development. Additional optimization of the informatics and IHC techniques may yield more powerful markers for identification of tumor origin. Expansion of the base of RNAseq data set to include rare tumors and metastatic specimens could further widen the usefulness and validity of this approach.

708 Mismatch Repair Deficiency (MMR-D) and Programmed Death-1 Expression in Gastric Adenocarcinomas
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Background: Immunohistochemical staining (IHC) for MMR (MLH1, MSH2, MSH6, and PMS2) is not routinely performed on gastric adenocarcinoma (GA) as is commonly done colon cancers, in which microsatellite instability and its high mutational frequency resulting in neo-antigens correlates with high expression of PD-L1. The clinical and pathologic features of MMR-deficient (MMR-D) GA are not well known. The goals of our study were to assess the prevalence of MMR-D in GA and its correlation with PD-L1 expression, whose expression offers an immunotherapy target with checkpoint inhibitors.

Design: 52 patients with GA who underwent resection from 1/12-6/16 were reviewed from the Beth Israel Deaconess Medical Center, Boston, MA and categorized as diffuse or intestinal-type. Tissue microarrays were constructed with representative areas from 38 diffuse and 14 intestinal tumors. IHC staining for PD-L1 was performed at the standard clinical approaches of V600E allele-specific PCR or NGS. All of these methods were considered absent if <1% of cells showed partial/complete membranous staining, low expression if 1-49% showed staining, and high if ≥49% showed staining.

Results: See table 1. Chi-square-test were applied.

Clinical and Pathologic Features of Intestinal-Type GA (n=38)

| Intestinal (n=38) | Diffuse (n=14) |
|------------------|---------------|
| Age (avg) (range) | 70 (40-92)     | 60 (37-81)     |
| Sex (% male) | 55% | 29% |
| MMR deficient | 26% (10/38) | 0% (0/14) |
| PD-L1 positive | 5% (2/38) | 7% (1/14) |
| High PD-L1 expression | 11% (4/38) | 0% (0/14) |
| NGS data (n=8) | Normal (1), FBXW7 (1), CTNNB1/GNAS/KRAS | TP53 (3), Normal (1), ATM (1) |
| Syndromes | 8% (3/38), Lynch (2), FAP (1) | 14% (2/14), CDH1 (2) |

Conclusions: The majority of GA cases were intestinal type (73%). Of these, MMR-D was noted in 26% and had higher frequencies of PD-L1 expression (p<0.001) compared to proficient cases, with only one case showing high expression (4%). The remaining cases showed diffuse-type (27%) and normal (47%) expression. In summary, MMR-D intestinal-type GA has higher frequencies of PD-L1 expression and may represent a potential immunotherapy target with PD-L1 inhibitors.

710 PD-L1 Specific Phenotypes of Colorectal Carcinomas Are Associated With Unique Molecular Alterations
Melanie K Johnella, Neal I Lindeman, Mikhail Livshyv, Amithab Sristavast, Brigham and Women’s Hospital, Boston, MA; Dartmouth-Hitchcock Medical Center, Lebanon, NH.

Background: Patients with inflammatory bowel disease (IBD) are at increased risk for colorectal cancer (CRC). IBD-associated adenocarcinomas (IBD-AA) may resemble conventional adenocarcinoma (ACA) but may also show a spectrum of phenotypes seldom seen in sporadic CRC. These include low grade tubuloglandular adenocarcinomas (LTGA), ACA arising in hypermucinous dysplasia, and well differentiated ACA rich in goblet cells. Our first aim was to analyze next generation sequencing NGS data to identify superior markers, whether these unique IBD-AA are associated with molecular alterations distinct from sporadic CRC.

Design: Inclusion criteria for IBD-AA were: ACA with the distinct features mentioned, those arising in a non-adenoma like DALN or those with multifocal dysplasia. Carcinomas with features resembling sporadic CRC were excluded unless one of the latter two criteria were fulfilled. DNA was extracted from 10 4u slides from FFPE blocks. Illumina TruSeq® was used to prepare the library for sequencing the exons of a 300 gene panel using an Illumina HiSeq 2000.

Results: 15 tumors met our criteria for IBD-AAs. Patient age ranged from 31-93 yrs (median=61). Six of 15 IBD-AAs showed a gastric phenotype similar to upper GI tract adenocarcinomas, 3 were associated with hypermucinous dysplasia, and 1 was a GI tract ACA. Two ACA with serrated dysplasia, two mucinous ACA and 1 conventional CRC were associated with either multifocal dysplasia or a non-adenoma like DALN. The number of mutations per case ranged from 1 – 53 (median: 7). The most frequent mutations were TP53 (11/15) spread across the entire morphological spectrum of IBD- AA vs 1/30 INAA (3/15), MECON (1) and IDH1 (2) were some low frequency mutations seen. ACA with a gastric phenotype showed TP53 (4/6), CDK2NA (2/6), ARID1A (1/6) and CDH1 (1/6), mutations similar to those in gastric carcinomas. ACA in hypermucinous dysplasia had TP53 (2/5) and ARID1B (3) mutations and one had an IDH1 mutation. One ACA showed a spectrum of phenotypes. Our cohort had low frequency mutations similar to sporadic CRCs including TP53 and ARID1A. The two mucinous CRC had no KRAS or BRAF mutations suggesting that these tumors may be distinct from conventional mucinous ACA.

Conclusions: TP53 mutations are highly prevalent in IBD-AA irrespective of histological tumor type and grade. IBD-AA that show a gastric phenotype also harbor molecular alterations similar to those seen in upper GI tract ACA. These findings have implications for neoplasia diagnosis and treatment for patients with CRC in the setting of IBD.

711 Identification of Unique Mutant Gene Profiles and Morphologic Features in a Large Cohort of BRAF-Mutant Colon Adenocarcinomas Using Next Generation Sequencing Approach
Ryan D Jones, David Dittmann, Alastair H Beanbur, Juwhee Gao, Guang-Yu Yang. Northwestern University, Chicago, IL.

Background: Although only approximately 10% of colorectal cancers (CRC) carry BRAF mutations, they harbor a worse prognosis with aggressive behavior. BRAF- mutant essentially excludes the possibility of Lynch Syndrome, but these commonly concomitant mutations in p53, PIK3CA and SMAD4 are frequently identified, 2) first passage of CRC cell lines typically lose MLH1 mismatch repair protein likely due to sporadic promoter methylation. Whether other cancer-related gene alterations in collaboration with mutant BRAF leads to carcinomas is not well known. This study utilizes next generation sequencing (NGS) together with immunohistochemistry (IHC) to analyze the mutation profile of cancer-related genes, expression of mismatch repair proteins, and morphology to characterize the key molecular and morphologic features in BRAF-mutant CRC.

Design: Through searching the large clinical CRC cohort from Northwestern Memorial Hospital (NMH) since 2014 (total 376 cases), 45 BRAF-mutant CRC were identified using the standard clinical approaches of V600E allele-specific PCR or NGS. All of these were further analyzed for key cancer-related gene mutation profile using NGS approach. Immunohistochemical stains were performed for MLH1, PMS2, MSH2, and MSH6 protein expression with proper controls. In our NMS cohort, the frequency of BRAF-mutant CRC was 12.0% (45/376). Among these 42/45 (93.3%) were BRAF V600E and 3/45 (6.7%) were non-pV600E including pN581E, pG606V, and pD594G. Concomitant mutations in other cancer-related genes in collaboration with mutant BRAF occurs in 3.3% (15/45) of those cases. The most frequent were TP53 (11/15) spread across the entire morphological spectrum of CRC. Our BRAF-mutant CRC exhibited loss of MLH1 and PMS2, with higher trends in cases with p53 WT (16/29, 55.2%) compared with p53-mutations (6/15, 37.5%). Morphologic analysis showed 82% (37/45) were right-sided, 89% (40/45) were high-grade (moderately to poorly differentiated), and 34% (15/45) had mucinous features.

Conclusions: Our results indicate that in addition to the common pV600E mutation, non-pV600E mutations are present in CRC and the frequency of BRAF mutation in CRC is 12.0%. The cancer-related gene mutation profile and IHC demonstrate that 1) concomitant mutations in p53, PIK3CA and SMAD4 are frequently identified, 2) first passage report on concomitant mutations in KRAS codon 14 and NRAS, and 3) loss of MLH1 expression is frequent but not as high as literature reports. All of these data imply BRAF mutation together with either loss MLH1 or other key gene mutations (PI3K, PIK3A and SMAD4) is crucial for driving carcinogenesis and targeting these mutations would be significant for developing therapeutic approaches.
712. Mucin Rich Variant of Traditional Serrated Adenoma (MrTSA): A Distinct Morphological Variant
Sangeetha N Kalimuthu, Stefano Serra, Sara Haji-Bakhhtiari, Richard Colling, Lai Min Wang, Runjan Chetty. UHN, Toronto, ON, Canada; UOIT, Oshawa, Ontario, Canada.
Background: Traditional serrated adenomas (TSA)s account for ~5% of serrated polyps, typically characterised by: ehyphic villiform architecture, eosinophilic cells with brush border, indented, flat-topped luminal serrations. However, a small subset has been observed to have a mucin-rich (Mr) component. We aimed to perform a clinical-pathological correlation to determine if MrTSA has unique features and ascertain differences with classic TSA (cTSA).

Design: A total of 156 TSA specimens were retrieved from the archives of 2 Pathology departments (UHN, Toronto and Oxford) from 2010-2016. Patient demographics and site were documented and 16 morphologic variables were evaluated including growth pattern, frequency of ephitic crypt foci (ECF), concurrence with other polyp types, type of serration, presence of dysmaturation/dystrophic goblet cells (GCs) or other secretory cells, degree of inflammation and type of dysplasia. TSA specimens with GCs (eosinophilic absorptive cell ratio at least 1:1) were arbitrarily classified as MrTSA. The number of ECFs were quantified as low (1-10x20 magnification field (MF)) and high (>10x20MF).

Results: Of 156 TSA, 23 fulfilled the criteria of MrTSA. More males had MrTSA (65%) than cTSA (55%) but no age difference noted. Whilst both groups showed a predilection for the left colon, MrTSA were more frequent in the right colon (39%) compared to cTSA (18%), (p=0.012). Five MrTSA (22%) and 70 cTSA (52%) were associated with other polyp types, respectively. Conventional adenomatous dysplasia was present in 4/23 MrTSA (low grade; 3; high grade; 1). Distinctive morphologic features of MrTSA were variable growth pattern (endophytic [9%], mixed [30%], exophytic [61%]) and significantly lower frequency of ECFs (61%) compared to cTSA (4%) (p=0.001). All MrTSA uniformly retain characteristic luminal serrations, at least focally. Also, inflamed endophytic MrTSA can simulate inflammatory polyps and mimic hamartomatous polyps when there is a predominance of GCs (>90%).

Conclusions: Our study highlights MrTSA as a distinct morphologic variant of TSA characterized by a miscellany of features including >50% GCs, fewer ECF (<10x20MF) and inflammatory polyps and mimic hamartomatous polyps when there is a predominance of GCs (>90%).

713. Complete Histopathologic Examination of Prophylactic Gastroectomy Specimens for CDH1 Germline Mutation: Is It Warranted in Routine Clinical Practice?
Dipti M Karamchandani, Zhaozhi Tang. Penn State Hershey Medical Center, Hershey, PA.
Background: Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant familial cancer syndrome. Germline CDH1 (E-cadherin) mutation is detected in 25-40% of tested families. Several prior studies performed complete histologic examination of these gastroectomy specimens in an attempt to characterize the microscopic lesions which may have implications for targeted endoscopic surveillance biopsies. However, no prior study has questioned the utility of histologic examination of the entire specimen in routine clinical practice. Presently, there is no uniform protocol regarding the extent of histologic examination and many academic institutions submit the entire stomach. In this study, we question the utility of complete histologic examination of the stomach in HDGC patients in routine clinical practice.

Design: A retrospective review of total gastroectomy specimens performed for CDH1 mutation from 2000-2015 revealed 5 prophylactic gastrectomies. 3 were entirely submitted with mapping and 2 (performed in 2004) were partially submitted. A complete re-review of all available slides for these cases was performed.

Results: No gross lesions were identified in any of the 5 specimens. The results of completely submitted specimens are tabulated in Table 1.

| Age | Sex | Total pieces | Pathology | Foci in fundus | Foci in mid- | Foci in antum |
|-----|-----|--------------|-----------|---------------|-------------|-------------|
| 1   | 33  | 510; 204     | In situ CA| 6             | 0           | 0           |
| 2   | 21  | 453,199      | IMC       | 27            | 8           | 0           |
| 3   | 55  | 430,170      | IMC       | 6             | 0           | 0           |

(Female, IMC-Intramucosal carcinoma, CA- carcinoma). For the 2 patients (35 year old male, 32 year old female) with incompletely submitted specimens (20 pieces and 25 pieces) , 7 9 and 7 foci of IMC respectively were found in fundus and body and none were seen in the antum. Furthermore characterisation as to the exact site of the body could not be delineated.

Conclusions: The patients with prophylactic gastrectomy in our series had multiple microscopic foci of in situ and IMC predominantly in the fundus and upper body. Noticeably, no foci in antum were seen. No submucosal or deeper invasion was seen in any of the above specimens. The results suggest that for routine clinical practice, entire submission of prophylactic gastrectomy in HDGC patients is probably not justified given the time and cost, and especially given that there is no change in tumor stage and further clinical management. We propose to target the fundus/upper body to get maximum number of clinically significant lesions.
716 Immunohistochemistry Based Molecular Classification of Gastric Cancer and Its Prognostic Significance
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Background: Gastric cancer (GC) is a heterogeneous disease entity, and substantial amount of efforts have been done to develop the classification of GC based on molecular biologic basis. However, analyzing the genomic signature is not always feasible, thus we aimed to i) validate a practical IHC based molecular classification of GC, and ii) assessed the Her2 status according to the classification.
Design: A total of 933 consecutive GC patients from two individual cohorts (N = 535 and 398, respectively) were classified into five groups as follows, using EBV in situ hybridization, MSI testing and IHC for E-cadherin and p53: group 1, EBV-positive gastric; group 2, MSI-high; group 3, MSS/EMLT-like; group 4, MSS/non-EMLT-like p53- IHC+; group 5, MSS/non-EMLT-like p53-IHC-. Her2 status was defined according to the results of Her2 IHC and SISH.
Results: The proportions of each group in whole study population are as follows: group 1, 1,848%; group 2, 8,616%; group 3, 13.20%; group 4, 28.08%; group 5, 41.28%. There was no significant discrepancy of the proportions between two cohorts. On survival analysis, group 2 had the best prognosis, sequentially followed by group 5, group 1, group 3, and group 4 in both study populations (P<0.001). Her2 positivity was observed in 6.9% of total population, and 93.1% of Her2 positive patients were in group 4 and 3, respectively.
Conclusions: While NKX6.1 is expressed more commonly in pancreatic and duodenal NETs compared to NETs from other GI sites, the low sensitivity and specificity in our hands raise concerns for the utility of this marker in determining the origin of a NET when the primary site is unknown.

717 YAP1 Is Commonly Overexpressed in FAP-Related Neoplasia
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Background: Yes associated protein-1 (Yap1), a regulator of the Hippo signaling pathway, is overexpressed in various neoplasms. The APC gene normally suppresses tumorigenesis by acting as a tumor suppressor, but when the primary site is unknown.

Design: Lesional tissue from 11 FAP patients (4 intestinal carcinomas, 7 colonic tubular adenomas (cTA), 4 desmoid tumors, small bowel adenomas (sbTA)), and 10 non-FAP patients (3 cTA, 4 FGP, and 4 sbTA) was examined. Normal tissue from FAP patients was also evaluated. IHC for Yap1 (Hi-125; sc-15407; Santa Cruz Biotechnology) was scored for negative, low, and high nuclear and/or cytoplasmic staining as described in prior studies. Beta-catenin IHC was evaluated for the presence of nuclear staining.

Results: In normal tissue from FAP patients, nuclear Yap1 staining was seen predominantly in colonic crypt bases, small bowel villi, and gastric pits. No FAP normal tissue showed high cytoplasmic Yap1 staining (Hi cyto). All FAP desmoid tumors and intestinal carcinomas showed high nuclear Yap1 staining (Hi nuc). Hi nuc was common in lesional tissue from both FAP/31.3%) and non-FAP cases (100%). Hi cyto was more common in hi nuc in non-FAP patients (50% vs. 0%) (Table 1).

718 The Clinical Significance of Active Colitis Following the Advent of Immunomodulator Therapy and Availability of PCR Based Microbiological Detection Panels
Heewon Kwak, Scott Maneshiek, Yera Tesc, Shu-Yuan Xiao, John Hart, Namrata Setia. University of Chicago, Chicago, IL.
Background: Active colitis is a morphologic pattern characterized by neutrophils in the lamina propria, neutrophilic cryptitis, or neutrophilic crypt abscesses in the absence of unequivocal chronic changes. Prior studies report infection as the most common cause of this pattern, followed by other entities: drug induced mucosal injury, incidental findings in screening colonoscopy, ischemia, and inflammatory bowel disease (IBD). Recently, there is an increased use of immunomodulators and the development of PCR based microbiologic panels (e.g. FilmArray® Gastrointestinal panel), which can simultaneously detect various bacterial, viral, and viral pathogens. This prospective study updates the clinical significance of biopsies diagnosed as “mild colitis”.

Design: Reports with a diagnosis of “colitis” were retrieved from our database from 2/2016, when a PCR infectious panel was first offered at our institution, to 9/2016. These cases were divided into active colitis or chronic colitis. Data collection included clinical symptoms, endoscopic findings, pertinent medication history, microbiologic PCR panel concurrently performed during the endoscopy (57) or resection (3), and follow up data up until resolution of their symptoms were reviewed on cases with active colitis without chronicity, when applicable.

Results: Of 560 cases diagnosed as “colitis”, 60 had colitis without unequivocal changes of chronicity (11%). Partially treated IBD comprised the largest subset (23%) of active colitis cases [CD 7, ulcerative colitis (UC) 7], and evolving CD (2) and UC (2). Concurrent infectious PCR panel was performed in 12 cases, with 3 positive results (Norovirus, Sapovirus, E. coli). Clinically, there were 10 cases of infectious colitis (17%), 3 which occurred in transplant patients. Other less common causes of active colitis included graft vs host disease (GVHD), diverticulitis, functional diarrhea, autoimmune disease, and ischemia. Unknown causes comprised 13% of cases with 5 screening colonoscopies performed in asymptomatic patients.

Conclusions: Partially treated early IBD was the most common cause of “mild colitis”, which includes both CD and UC in our subset of cases. Immune modulators should be considered in the differential for mild colitis. Unique infectious etiologies can be detected using PCR based microbiologic panels. Previously unreported causes of mild colitis include GVHD and pancreatic insufficiency.

719 HER2 Expression Is Predominantly Negative in GEJ and Gastric Adenocarcinoma with Signet Ring Cell Differentiation: Study of 346 Cases
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Background: Currently there are no CAP/ASCP/ASCO-approved guidelines for HER2 testing and scoring of GEJ and gastric cancers. The draft guidelines from 2015 have raised the issue of universal testing of all gastric and esophageal adenocarcinomas. A low prevalence (1-7%) of HER2 expression has been reported in diffuse-type gastric carcinoma. We investigated the relationship of HER2 status and clinicopathologic features of GEJ and gastric adenocarcinomas with particular emphasis on histologic type, including signet-ring cell differentiation.

Design: GEJ and gastric adenocarcinomas from 05/2007-07/2016 were identified from 2 institutions. HER2 immunohistochemistry (IHC) and HER2 S/FISH amplification were assessed using CAP/ASCP guidelines. Select cases used mass spectrometry (OncoPlex) or next generation sequencing (NGS, FoundationOne®) to determine HER2 protein quantitation or amplification, respectively. Equivocal HER2 IHC was referred to S/ FISH, mass spectrometry, or NGS. Results were compared with age, sex, tumor size, histologic type [Lauren classification and presence or absence of signet ring cells (signet ring cell differentiation)], histologic grade, tumor location, and T, N, and M stage, when available. Univariate analysis was performed to determine whether the above variables were predictive of HER2 overexpression/amplification (HER2 positive).

| Table 1: Distribution of NKX6.1 Staining. |
|----------------------------------------|
| Site of NET | Total number of cases | Total number of cases with ≥5% NKX6.1 Stain | % Positive |
|----------------------------------------|
| Peyer’s patches | 35 | 32 (91%) | 91% |
| Duodenum | 12 | 11 (92%) | 92% |
| Small Bowel | 60 | 52 (87%) | 87% |
| Stomach | 18 | 16 (89%) | 89% |
| Colon | 26 | 24 (92%) | 92% |
| Rectum | 6 | 4 (67%) | 67% |
| Peyer’s patches and Duodenum | 126 | 91 (72%) | 72% |
| Others | 80 | 20 (25%) | 25% |

Conclusions: While NKX6.1 is expressed more commonly in pancreatic and duodenal NETs compared to NETs from other GI sites, the low sensitivity and specificity in our hands raise concerns for the utility of this marker in determining the origin of a NET when the primary site is unknown.

| Table 2: ANNUAL MEETING ABSTRACTS |
|------------------------------------|
| HI cyto Yap1 | HI nuc Yap1 | Nuclear β-catenin |
|------------------------------------|
| Normal | Non-FAP | FAP | Non-FAP | FAP | Non-FAP | FAP | Non-FAP |
| Normal | 0/3 (0%) | n/a | 3/3 (100%) | n/a | 0/3 (0%) | n/a |
| Abnormal | 0/3 (0%) | n/a | 2/3 (67%) | n/a | 0/3 (0%) | n/a |
| βTA | 0/4 (0%) | 2/4 (50%) | 3/4 (75%) | 4/4 (100%) | 2/4 (50%) | 1/4 (25%) |
| FGP | 4/4 (100%) | 4/4 (100%) | 4/4 (100%) | 0/4 (0%) | 0/4 (0%) |
| CA | 0/7 (0%) | 0/3 (0%) | 0/7 (50%) | 3/3 (100%) | 1/7 (14%) | 3/7 (43%) |
| Desmoid | 3/4 (75%) | n/a | 4/4 (100%) | n/a | 4/4 (100%) | n/a |
| Intestinal | 3/4 (75%) | n/a | 4/4 (100%) | n/a | 2/4 (50%) | n/a |
| Total | 18/32 (56.3%) | 6/11 (54.5%) | 28/32 (87.5%) | 11/11 (100%) | 9/32 (28.1%) | 2/11 (18.2%) |

Conclusions: YAP1 is commonly overexpressed in various neoplastic lesions from FAP patients including intestinal carcinoma and desmoid tumors. YAP1 could potentially serve as a valuable biomarker in FAP-related neoplasia, but larger studies are needed to evaluate the trends noted here.
Results: Of the 346 cases identified, 290 were biopsies and 56 were excisions. Mean comprised 74% (the mean age was 63 years (range 16-88 years). Histologic types identified included: intestinal (66%), diffuse (25%) and mixed (9%). Overall, 61/346 (17.6%) of cases were HER2 positive. Intestinal, diffuse, and mixed types comprised 89%, 11%, and 0% of HER2 positive cases, respectively. Only 1/46 cases with signet ring cell differentiation was HER2 positive (B/C). Intestinal type and moderate grade were predictive of HER2 positivity [OR 5.09, 95% CI 1.94-13.35, p<0.01; OR 2.51, 95% CI 1.29-4.91, p<0.01]. Signet ring cell differentiation and poor grade were predictive of the absence of HER2 [OR 11.02, 95% CI 4.89-26.5, p<0.01; OR 2.33, 95% CI 1.20-4.67, p<0.01].

Conclusions: Expression/amplification of HER2 is unlikely in the presence of signet ring cell differentiation. Intestinal type and moderate grade were predictive of HER2 positivity, while poor grade was a negative predictor. Based on our findings, we recommend incorporation of signet ring cell differentiation in the upcoming guidelines for HER2 testing in GEJ and gastric cancers.

720 Site-Specific Molecular Alterations in Colorectal Carcinoma: KRAS Mutations Are More Frequently Identified in Celiac Adenocarcinoma Compared to Other Location Subsites

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Background: Recent literature indicates that colorectal cancer (CRC) can be subdivided into clinically relevant subtypes based on mutations in BRAF and KRAS and DNA mismatch repair (MMR) protein abnormalities. However, CRC subsite specific molecular differences have not been fully elucidated.

Design: 413 consecutively resected CRCs over a 2-year period were analyzed for mutations in BRAF and KRAS and for MMR protein abnormalities by immunohistochemistry. The frequencies of molecular and histologic features as well as histologic subclassification (KRAS wild-type/BRAF-mutant/MMR proficient, KRAS-mutated/MMR proficient, BRAF-mutated/MMR proficient, and MMR protein deficient regardless of KRAS and BRAF status) were examined along bowel subes.

Results: The table details the differences in molecular subtypes stratified by tumor subsites. Cecal tumors were more often categorized as the KRAS-mutated/MMR proficient molecular subtype (43%) compared to other tumor subtypes within the right colon (24%) (p=0.02) and compared to samples from the left colon (3%) (p<0.04). BRAF-mutated/MMR proficient status was more often seen in cecal tumors (5%) and other tumor subites in the right colon (1%) compared to tumors of the left colon/rectum (1%) (p=0.01). Tumors of the left colon/rectum more frequently demonstrated concurrent KRAS wild-type, BRAF wild-type, and MMR proficient status (62%) compared to cecal tumors (28%) and other tumor subites of the right colon (37%) (p<0.0001).

Conclusions: Our findings indicate there are significant site-specific differences in molecular subtypes in CRC. In particular, the findings challenge the dichotomous division of CRC into right versus left colon/rectum and suggest that cecal tumors represent a potentially unique subtype of CRC characterized by a high frequency of KRAS mutations compared to other colorectal subites.

721 Squamous Morule in the Pseudo-invasive Foci of Colon Adenomatous Polyp Morphologically Mimics Invasive Carcinoma

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Background: Colorectal adenoma can show focal squamous differentiation or squamoid morules in colonic adenomatous polyps. Squamoid morules in colonic adenomatous polyps can mimic invasive carcinoma when present in the pseudo-invasive foci. Pathologists should be aware of its presence and morphology in the colorectal adenoma to prevent over diagnosis of invasive carcinoma.

722 Association of Micropapillary Architecture and High Tumor Budding with Prognosis in Patients with Stage III Colon Cancer from a FOLFOX-Based Adjuvant Chemotherapy Trial: NCTCG H10147 (Alliance)

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Background: We hypothesized that high tumor budding and micropapillary architecture would be individually associated with poor disease-free (DFS) and overall survival (OS) and that the presence of both features would have an additive effect in colon carcinoma patients.

Design: Histologic tumor sections from Stage III colon cancer patients (N=1704) treated in a randomized trial of adjuvant FOLFOX+-/-cetuximab were analyzed for micropapillary architecture (considered present [≥15%] or absent) and tumor budding (200x field; ≥10 buds = high budding). Chi-squared or Wilcoxon Rank sum tests were used to assess the associations between each variable, as well as KRAS, BRAF, and mismatch repair status (MMR). Prognosis was evaluated using adjusted multivariable Cox models for DFS and OS.

Results: The median tumor bud count was 5 and high tumor budding was detected in 506 tumors (29.7%). Micropapillary architecture was identified in 380 tumors (22.3%) in amounts ranging from 1 to 90% of tumor area. Both features of interest were seen in 199 patients (11.7%); 1016 (59.6%) had neither. Either presence of micropapillary or high tumor budding were each associated with T3/T4 vs 1/2, N2 vs N1, high vs low grade, and proficient MMR vs deficient MMR. High tumor budding was associated with proximal site, mutations in KRAS or BRAF, and low tumor infiltrating lymphocytes. High tumor budding was associated with shorter DFS (HR 1.29, p=0.009) and shorter OS (HR 1.37, p=0.002). Micropapillary architecture was not significantly associated with DFS or OS. DFS of both features did not differ from those with only one feature, but patients with both features had shorter OS compared to those with only positive micropapillary architecture (HR 1.46, p=0.044).

Conclusions: High tumor budding and micropapillary architecture are both associated with poor patient outcomes. Tumor budding was a significant and independent predictor of poor disease outcomes. Support: U10CA1808820, U10CA1808821, U10CA1808835, U10CA1808882, and U10CA1808888. ClinicalTrials.gov Identifier: NCT00079274.
The mean maximum ABC in controls was 1.79, which was less than both ACD and GFD (p=0.001 and p=0.019 respectively). Completely flat lesions (mean: 6.44) also showed a higher ABC compared to non-flat lesions (mean: 4.87; p=0.04).

**Conclusions:** Crypt ABC is markedly elevated in ACD and decreases significantly with GFD, however it does not achieve normalcy. In ACD patients, flat mucosa (Marsh 3C) is associated with a higher ABC than all other Marsh lesions. It is likely that crypt apoptosis is important in the mucosal flattening of celiac disease.

### 724 Risk Factors of Lymph Node Metastasis in T1 Colorectal Cancer: Tumor Budding Is a Reliable Pathologic Indicator Than Depth of Submucosal Invasion

**So Jeong Lee, Do Your Park, Kyung Un Choi, Gi Young Huh, Chang Hun Lee, Ahrong Kim, Young Keum Kim, Chang Su Hwang. Pusan National University Hospital, Busan, Seo-Gu, Republic of Korea.**

**Background:** With development of endoscopic treatment modalities for T1 colorectal cancer (CRC), it is important to accurately determine risk of lymph node (LN) metastasis in T1 colorectal cancer (CRC). We investigated risk factors of lymph node metastasis in T1 CRC to develop safe guideline for endoscopic resection of T1 CRC.

**Design:** Study cohorts included 133 cases of T1 CRC from January 2010 to June 2016. We reviewed clinicopathological features of all cases, including gross type, histological differentiation, lymphatic invasion, vascular invasion, and tumor budding. We also measured submucosal invasion depth (SIM) by macroscopic type and muscularis mucosae status.

**Results:** Of 133 cases of T1 CRC, 16 cases showed LN metastasis. Interestingly, there are no statistically different depth of submucosal invasion between LN(+) (2246±1079.660) and LN(-) (3588±1819.056) groups (SIM μ± standard deviation, p=0.725). Furthermore, there was no association between lymphovascular tumor emboli and LN metastasis. Presence of tumor budding and higher number of tumor budding are reliable indicator for LN metastasis in T1 CRC (p<0.005). Presence of adenoma component is negative indicator for LN metastasis (p=0.036).

**Conclusions:** We found tumor budding is a reliable indicator than depth of submucosal invasion and recommend careful identification of tumor budding in routine surgical practice of T1 CRC.

### 725 Loss of Cellular Histone Modifications in Pancreatic Adenocarcinoma

**Hsing-Yi Li, Aaron G. Harper, Danqi Chen, Chunyaon Jin, Steve Xie. Downstate Medical Center, Brooklyn, NY; New York University, Tuxedo Park, NY; Kings County Hospital, Brooklyn, NY.**

**Background:** A recent comprehensive integrated genomic analysis of 456 pancreatic ductal carcinomas (PDC) identified 32 significant mutated genes that aggregate into 10 molecular mutational mechanisms. Histone modification is determined as one of these important mechanisms and the mutated genes identified in 24% of the cases include KDM6A, SETD2 and ASCOM complex members MLL2 and MLL3. KDM6A is a histone demethylase that specifically demethylates “Lys-27” of histone H3 (H3K27me3), which is associated with repression of gene activity. ASCOM possesses histone methyltransfer activity that specifically methylates “Lys-4” of histone H3 (H3K4Me3), which is associated with activation of gene activity. These mutated genes therefore might lead to global changes in H3K27me3 and H3K4Me3, which could be used as diagnostic/prognostic biomarkers of pancreatic ductal carcinomas.

**Design:** Here we investigated cellular expression levels of H3K27me3 and H3K4Me3 in pancreatic adenocarcinomas as well as nonneoplastic pancreatic tissues, aiming to explore the diagnostic/prognostic values of epigenetic markers in pancreatic carcinogenesis.

**Results:** Twelve pancreatic adenocarcinoma samples were examined. Immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissue blocks using antibodies against H3K27me3 and H3K4me3. The staining intensity of cancer tissues was quantified by the NIH ImageJ software and compared to the staining intensity of peritumoral normal ducts. The cellular levels of both H3K27me3 and H3K4me3 were dramatically downregulated in all pancreatic adenocarcinoma samples we tested compared with peritumoral normal ducts. The difference in the levels of H3K27me3 and H3K4me3 between normal pancreatic ducts and pancreatic adenocarcinomas was statistically significant (p=0.05).

**Conclusions:** H3K27me3 and H3K4me3 are associated with gene inactivation and activation, respectively. Thus, aberration in these modifications might be involved in pancreatic carcinogenesis through changing gene expression. In this preliminary study, we found significantly decreased levels of H3K27me3 and H3K4me3 in all twelve samples, suggesting that the loss of these modifications might be used as biomarkers for pancreatic adenocarcinoma. The correlation between the cellular levels of these histone modifications and clinicopathologic parameters and clinical outcomes are currently under investigation in a larger scale study.
728  Morphologic and Immunohistochemical Characterization of Sessile Serrated Adenomas with Dysplasia
Cheng Liu, Neal Walker, Mark Bettington, Christophe Royst, Barbara Leggett, Vicki Whitehall. QIMR Berghofer Medical Research Institute, Brisbane, Australia; Envi Speciai Pathologists, Brisbane, Australia; Royal Brisbane and Women's Hospital, Brisbane, Australia; University of Queensland, Brisbane, Australia.
Background: Dysplasia occurring in sessile serrated adenoma (SSA) is uncommon and it heralds rapid progression to invasive carcinoma. The WHO definition for SSA with dysplasia (SSAD) divides it into conventional and serrated types, but it has become apparent that the morphology of SSADs falls on a spectrum and some variants are difficult to classify using current criteria. We undertook a comprehensive review of all SSAD diagnosed over a four-year period to fully characterize these variants.
Design: SSADs diagnosed at a specialist gastrointestinal pathology practice between 2012 and 2016 were retrospectively identified through database search. A total of 256 SSADs were reviewed and classified based on architectural and cytologic features.
Results: When more than one type of dysplasia was present in an SSAD, they were classified separately. MLH1 immunohistochemistry was performed in all cases. Results: We identified several distinct variants of SSAD. Most notable was the “minimal deviation” variant, present in 12 of 254 cases, which demonstrated only subtle architectural abnormalities compared with the background non-dysplastic SSA. These included gland crowding, gland dilatation, horizontal growth of glands, and excessive luminal serrations or a smooth luminal profile. There was no cytologic atypia. A dysplastic interpretation was supported by MLH1 loss and the presence of overt dysplasia elsewhere in the same biopsy. Other variants displayed similarities to traditional serrated adenoma (TSA) or conventional adenoma, and thus had the potential for both under- and over-diagnosis.

729  Gene Expression Profiling in Collogenous Colitis: Toward a Better Understanding of the Disease
Qingqing Liu, Huai-Bin Mado Ko, Hongta Zhu, Alexandre D Polidori, Noam Harpaz. Ichan School of Medicine at Mount Sinai, New York, NY.
Background: Collogenous colitis (CC) is a common but enigmatic diarrheal disorder that is thought to result from dysregulated mucosal immune responses to unknown luminal agents in genetically susceptible individuals. Its association with immune dysregulation is suggested epidemiologically by its close associations with celiac disease and other autoimmune disorders. We aimed to probe its pathogenesis by means of gene expression profile analysis with a focus on inflammatory and immunological pathways.
Design: mRNA was isolated from colonic biopsies of 13 histologically confirmed patients with CC and analyzed by the NanoString nCounter gene expression assay. The analysis included a comparison of mucosa with and without abnormal subepithelial collagen (“involved” and “uninvolved”) (N=5), pooled biopsies of involved mucosa of additional patients (N=8) and pooled biopsies from normal controls (N=8). Assays targeted 778 human genes, 594 differentially expressed in inflammatory conditions. The raw expression data were normalized using nSolver Analysis Software 3.0 and a dataset of gene expression ratios for CC vs controls was generated.
Results: Our results showed increased expression of matrix-metalloproteinases (MMP-1, 3, 7 and MMP-9) in involved samples, confirming the results of a prior study. Interferon gamma (INFγ) was markedly upregulated (31X) in all cases of CC and was accompanied by corresponding upregulation of its downstream genes including STAT1 (3.48X) of the Jak-STAT pathway, multiple members of the T-lymphocyte chemokine/receptor (C-X-C motif) ligand family (CXCL5, 5.07-13.90X) and their receptors (CXCR5, 2.79-7.51X). Additionally, we noted enrichment of mRNA expression for HLA-DOA (1.12X) and HLA-DQB1 (1.98X) in our CC population, a feature shared with celiac disease. Each of these findings was observed in both involved and uninvolved mucosa of CC cases.
Conclusions: The colon mucosa in CC is characterized by enhanced expression of a limited repertoire of immunological and inflammatory genes. The nature of the corresponding pathways may help guide further investigations into its etiology.

730  Diagnostic Value of Stage-Specific Expression of SMAD4 and TP53 in Barrett’s-Associated Neoplasia
Qingqing Liu, Huai-Bin Mado Ko, Hongta Zhu, Alexandre D Polidori, Noam Harpaz. Ichan School of Medicine at Mount Sinai, New York, NY. 
Background: Accurate classification of biopsies with Barrett’s-associated high-grade dysplasia (HGD) and invasive adenocarcinoma carries important therapeutic implications but can be challenging. Histological criteria such as solid or cribiform growth pattern, intranuclear necrosis and ulceration have proven useful, albeit imperfect, in predicting the presence of invasion in resection specimens. A recent cancer genome sequencing study of Barrett’s metaplasia, dysplasia and adenocarcinoma reported that inactivating mutations in the p53 and SMAD4 genes occurred uniquely in HGD and carcinoma in a stage-specific manner, i.e., p53 in >70% of HGD and carcinoma and SMAD4 in 10% of carcinoma only. To our knowledge these findings have not been exploited diagnostically by immunohistochemical means.
Design: TP53 and SMAD4 immunostaining were performed on a series of 20 specimens, with HGD and 10 biopsies or resection sections with intramuscular adenocarcinoma (IMC). All diagnoses were confirmed by a group of 5 GI pathologists at a divisional consensus conference and based on clinical follow-up. Wild-type TP53 expression was defined as heterogeneous nuclear expression of ≥ 2 or less and mutant-type expression as absent expression or homogeneous overexpression of ≥ 2 or more. Wild-type SMAD4 expression was defined by nuclear expression comparable to that in the surrounding normal tissue and mutant-type expression by absent expression.
Results: Mutant-type TP53 expression occurred in 8 of 10 cases of HGD (80%) and in 10 of 10 cases of IMC (100%). In contrast, mutant-type SMAD4 expression occurred in 9 of 10 cases of HGD and in 3 of 10 cases of IMC (30%) (p=0.031, chi square method).
Conclusions: Our results are compatible with the findings reported by cancer genome sequencing. Stage-specific immunostaining for SMAD4, if confirmed in larger studies, may afford a valuable adjunct to conventional histological criteria in achieving accurate diagnoses of invasive Barrett’s adenocarcinoma.

731  Incidence and Prognosis of Extramural Venous Invasion in Small Intestine Neuroendocrine Tumors
Qingqing Liu, Huai-Bin Mado Ko, Hongta Zhu, Noam Harpaz, Alexandre D Polidori. Ichan School of Medicine at Mount Sinai, New York, NY.
Background: Extramural venous invasion (EVI) is a well-established independent prognostic factor in colorectal carcinoma and has been linked to distal hematogenous spread (e.g., to the liver), thus influencing the clinical decision to administer adjuvant chemotherapy. However, the prognostic significance of EVI in small bowel neuroendocrine tumors (NET) has not been extensively studied and it is not routinely assessed or reported.
Design: We retrospectively reviewed resected small bowel NETs at our institution over a 6 year period (2010-2016). H&E slides were independently scored by two pathologists for the presence of EVI, defined as the unequivocal presence of NET deposits within the lumen of large subserosal veins, the latter being in close proximity to large arteries. Elastica van Gieson (EVG) was selectively used as an adjunct method in equivocal cases. Information on clinicopathologic features, including the presence of liver metastases, was obtained from pathology reports and medical records. Fisher’s exact test was used to determine statistical significance (defined as P<0.05). Of 77 patients with primary small bowel NETs, 36 men; median age 62 years, range: 31-84 years; 3 duodenal, 31 ileal, and 43 small bowel, median age 62 years, range: 31-84 years; 3 duodenal, 31 ileal, and 43 small bowel, not otherwise specified were included in the study. EVI was identified in 42 cases (54.5%), 31 of which (73.8%) had liver metastases either at the time of resection or subsequently developed. This incidence was significantly higher than that observed in patients without evidence of EVI (N=35), only 6 of whom (17.3%) had liver metastases (P<0.0001). Presence or absence of EVI did not correlate with pathologic tumor stage (pT) or lymph node status (pN) (P>0.05).
Conclusions: Our data demonstrate that EVI is commonly present in small bowel NETs and strongly correlates with the presence of liver metastases. Therefore, its evaluation is critical during the pathologic examination of resection specimens with these tumors and should be assessed in combination with adjuvant techniques such as EVG, if necessary. Moreover, EVI status may need to be included in the pathology reporting guidelines for small bowel NETs.

732  Expression of PD-L1 in Colorectal Carcinoma (CRC) Primarily Occurs in Stromal/Immune Cells at Tumor-Stroma Interface (TSI), and Is Associated with High Tumor-Infiltrating Lymphocytes (TILs) Irrespective of the Microsatellite Instability (MSI) Status or the Molecular Mechanism of MSI
Sandy Liu, Jaclyn Hochman, Neil Segal, Jessica Smith, Deepthi Rao, Arnold Markowitz, Martin Weiser, Efsevia Vakiani, David S Klimstra, Zsofia Stadler, Jinru Shia. Memorial Sloan Kettering, NY, NY. 
Background: The expression of programmed death-ligand 1 (PD-L1) has been characterized in colorectal carcinoma (CRC). It remains to be determined whether PD-L1 expression is driven by MSI-H or TILs. It is associated with high tumor-infiltrating lymphocytes (TILs) irrespective of the Microsatellite Instability (MSI) status or the Molecular Mechanism of MSI.
Design: We studied PD-L1 expression via immunohistochemistry (IHC) on whole sections in the following 5 groups of cases (n=78%): 1) 16 MSI-H CRCs from 16 Lynch-syndrome patients with mismatch repair (MMR)-gene-germline mutation; 2) 21 sporadic MSI-H CRCs with MLH1-promoter methylation; 3) 13 MSI-L CRCs without germline-mutation or MLH1-methylation; 4) 13 microsatellite-stable (MSI-) CRCs with unusually high TILs (MSI-ITIL); and 5) 15 MSS CRCs with low TILs.
(MSL-low-TIL). The staining intensity for both markers was scored 0–3+. The extent of PD-L1-staining was seen as % of TSI area showing positive staining, and the extent of PD-1-stained-TILs was semi-quantitatively graded (0–3).

**Results:** The mean “TILs/10HFPs” ranged 27–57 in the 3 MSI-H groups, and was 40 in MSL-it-TIL and 3 in MSL-low-TIL groups (p<0.02). IHC expression of PD-L1 was primarily present on stromal lymphocytes/immune cells at TSI; less commonly, it was also seen within tumor cells. The intensity and expression of PD-L1 at TSI were not different across the 3 MSI-H groups and the MSL-it-TIL group (p>0.33). However, both were significantly higher in all 4 groups (individually or collectively) when compared to the MSL-low-TIL group (p<0.001). Similarly, the intensity and extent of PD-1-staining in TILs did not differ across the MSI-H and MSL-it-TIL groups (p>0.15), but in the latter 4 groups, the PD-1 intensity was significantly higher when compared to MSL-low-TIL group (p<0.001).

**Conclusions:** Our results reaffirm prior studies that expression of PD-L1 occurs in a subset of MSI-H CRCs. Further, we demonstrated for the first time that PD-L1 expression is a function of high TILs irrespective of the MSI status or the molecular mechanism causing MSI. The common perception that MSS tumors lack PD-L1 expression is likely due to the low incidence of TILs in these tumors. Our observations bear potential implication in the determination of patient-selection method for anti-PD1 trials for CRC.

**733 Calretinin Positivity in Poorly Differentiated Colorectal Carcinoma: A Diagnostic Pitfall**

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**Background:** Calretinin, a calcium-binding protein encoded by the CALB2 gene and involved in calcium signaling, is commonly used as an immunohistochemical marker for the diagnosis of mesothelioma. We have recently encountered a poorly differentiated CRC, which was negative for calretinin IHC positivity in colorectal carcinoma (CRC).

**Design:** A total of 257 CRCs, involved in calcium signaling, is commonly used as an immunohistochemical marker for the diagnosis of mesothelioma. We have recently encountered a poorly differentiated CRC, which was negative for calretinin IHC positivity in colorectal carcinoma (CRC).

**Results:** In total, positive calretinin staining was observed in 3 of the 257 (1%) CRCs. Along with various clinico-pathological characteristics.

**Conclusions:** Calretinin IHC positivity can be observed in a small but finite proportion of CRCs. Calretinin-positive CRCs share clinico-pathological characteristics with MSI-H tumors. Awareness of this phenomenon can avoid the diagnostic pitfall of misinterpreting poorly differentiated colorectal carcinomas as mesotheliomas on the basis of calretinin positivity and prompt additional work-up to allow accurate tumor classification.

**734 Next Generation Sequencing Identifies Mutational Distinction Between Primary and Metastatic Colorectal Carcinoma: Potential Therapeutic Implications**

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**Background:** Colorectal carcinoma (CRC) is a common and aggressive malignancy for which standard chemotherapy is of limited benefit in the metastatic setting. Recently, targeted next generation sequencing (NGS) has emerged as a clinical tool for the identification of actionable gene mutations in order to triage advanced cancer patients to alternative targeted therapies. It is unclear whether primary CRCs or their metastases should be sequenced for NGS. We explore the mutational distinctions between paired primary and metastatic tumors.

**Design:** A total of 45 formalin-fixed, paraffin-embedded tumors were sequenced from 14 patients, including 15 primary tumors, 10 regional lymph node metastases, 18 distant organ metastases (H&N), and 3 recurrences at anastomotic sites. Samples were sequenced using the 50-ncro AmpliSeq cancer panel v2, targeting 2855 hotspot mutations.

**Results:** Ten of 14 patients (72%) had identical mutational profiles in primary and metastatic sites, 2 (14%) had similar but not all variants in common among different sites, and 2 patients (14%) had sites with entirely unrelated hotspot patterns. In total, 11 of the nonidentical cases, clinically relevant (actionable) mutations were found in metastases that were not present in primaries. Across all patients, 87 mutations were identified involving 10 genes: TP53, APC, KRAS, PIK3CA, BRCA1, BRCA2, SETD2, PTEN, SMAD4, and ATM. Seventy-four mutations (85%) were concordant between primary tumors and DM.

**Conclusions:** Our pilot study indicates that most patients have identical mutations in their paired primary and metastatic CRCs, and thus either may be suitable for extension of this study to a larger patient cohort (ongoing) is necessary before broader conclusions are drawn, a provisional proposal is that genetic profiling of one or more metastases should be considered in the setting of resistance to therapy chosen based on the genetic profile of the primary CRC.

**735 The Autophagy-Associated ATG16L1 Gene Polymorphism Affects Outcome of Gastric Adenocarcinoma Patients**

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**Background:** Autophagy-associated ATG16L1 gene is known to affect a range of host immune response to pathogens. A non-synonymous single nucleotide polymorphism (SNP) of ATG16L1, Thr300Ala (T300A), is one of the main Crohn disease (CD) susceptibility alleles. Previous studies have shown that mice with T300A Thr300A knock-in are associated with increased production of inflammatory cytokines albeit reduced pathogen clearance. Given the importance of host immunity to cancer, we hypothesized that host ATG16L1 T300A genotype correlates with clinical outcome in cancer.

**Design:** Consecutive gastric adenocarcinoma patients who underwent resection between 2006 and 2012 were included. For each patient, genomic DNA was extracted from formalin-fixed paraffin-embedded noncancerous tissue and analyzed by quantitative PCR for ATG16L1 T300A genotype. The risk allele for ATG16L1 T300A (as per CD susceptibility) is G; the wild-type allele is A. The patients’ genotypes were correlated with demographics, various histologic features, and clinical outcome.

**Results:** A total of 173 patients were genotyped. Among them, 126 (73%) carried the risk allele G, including 44 (25%) homozygous GG and 82 (47%) heterozygous GA genotypes. Significantly higher proportions of Caucasian patients carried the G allele(s) compared with those of African American patients (111/135, 82% vs 70/20, 35%, P = 0.001). Univariate outcome analysis correlation identified homozygous GG patients had significantly longer overall survival than patients with either GA or AA genotypes (median and range: 40.6 months [4.8–99.2] vs 16.4 [0.5–96.5] vs 21.4 [0.7–106.0], P = 0.019). Importantly, in the subset of patients (75/173, 43%) who did not receive additional therapy, patients with homozygous GG genotype still had significantly longer overall survival than the other genotypes by multivariate analysis adjusting for clinical stage (hazard ratio: 0.279, 95% confidence interval: 0.108 – 0.719, P = 0.008. The ATG16L1 T300A genotype did not correlate with age, gender, histologic grade, depth of invasion, nodal metastasis or recurrence-free survival (P > 0.05 for all).

**Conclusions:** Gastric cancer patients carrying 2 ATG16L1 T300A risk (G) alleles are associated with improved overall survival, suggesting that ATG16L1 may have dichotomous effects in immunity against infection and cancer. Additionally, genotyping gastric cancer patients may provide additional insight for management and can be incorporated into standard patient care.

**736 Characterization of Dysplasia in Non-Targeted Colorectal Biopsies in IBD**

Yihong R Ma, Huai-Bin Mabel Ko, Hannah J Sreedhar, Alexandros D Polydorides, Hongfa Zhu, Noam Harlap. Icahn School of Medicine at Mount Sinai, New York, NY; Washington University, St. Louis, MO.

**Background:** Colorectal dysplasia complicating IBD is notoriously difficult to detect by standard endoscopy. Surveillance for dysplasia traditionally employs both random biopsy sampling and targeted biopsies of suspicious visible lesions. Recent studies suggest that most dysplasia is visible under optimal conditions, e.g., high-definition optics and/or chromoendoscopy, leading some authorities to question the value of random biopsies altogether. It follows that more information is needed regarding the prevalence, biological characteristics and clinical significance of non-targeted dysplasia (NTD). We sought to determine the histological characteristics of NTD as a basis for future studies.

**Design:** Biopsies with NTD were identified on the basis of careful review of all available random biopsies altogether. It follows that more information is needed regarding the prevalence, biological characteristics and clinical significance of non-targeted dysplasia (NTD). We sought to determine the histological characteristics of NTD as a basis for future studies.

**Results:** Forty-six exams of 39 patients (28 UC, 10 Crohn’s, 1 indeterminate) yielded 77 NTDs. Mean disease duration was 18.3y. Thirteen (29%) procedures were performed on the basis of careful review of all available random biopsies altogether. It follows that more information is needed regarding the prevalence, biological characteristics and clinical significance of non-targeted dysplasia (NTD). We sought to determine the histological characteristics of NTD as a basis for future studies.

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737  Inflammatory Polyposis in Patients with Inflammatory Bowel Disease
Yihong R Ma, Huai-Bin Mabel Ko, Hongta Zha, Noam Harpaz, Alexandros D Polydorides. Icahn School of Medicine at Mount Sinai, New York, NY.
Background: Patients with inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn disease (CD), often develop inflammatory polyps (IPs) which can be large and/or multiple and may hinder successful endoscopic surveillance. The term inflammatory polyposis (IPS) has been used to indicate the presence of multiple or diffuse IPs, however exact criteria (number, size, or extent) have not been consistently defined. We sought to identify cases of IPS and determine their clinical outcomes, particularly in terms of the presence of incidental (previously unknown) neoplasia.
Design: Surgical resection specimens from patients with IBD were reviewed during a 10 year period (2006-2016) and cases of IPS were identified as those having diffuse, innumerable, carpeting, or multiple (more than 5) IPs described in the gross description or diagnostic comment, and/or seen in endoscopic images or gross specimen pictures. A control non-polypolyposis (NPS) group (with no, or at most 5, IPs) was identified from the same patient population. For patients with multiple surgeries, only the earliest identified resection was included. Clinicopathologic data (age, sex, IBD type, and highest grade of dysplasia) were recorded. Cases with dysplasia and/or carcinoma diagnosed on prior endoscopic biopsies were excluded.
Results: Fifty-three cases of UC patients with IPS were identified [55 (66%) men, 18 (34%) women, mean age 42 years (range: 19-71)] and 4 (6%) had incidental colonic dysplasia (2 low-grade, 1 high-grade). No carcinomas were found. None of these variables were statistically significant when compared to a control group of 66 NPS UC cases, among which 2 (3%) had low-grade dysplasia. Forty nine cases of CD patients with IPS were identified [50 (61%) men, 19 (39%) women, mean age 38 years (range: 19-69)] and 2 (4%) had incidental low-grade dysplasia (one ileal, one colonic). These were similar to a control group of 154 NPS CD cases, where 5 (3%) incidental neoplastic lesions were identified, including 2 colonic dysplasias (one low-grade, one high-grade) and 3 ileal adenocarcinomas.
Conclusions: IPS patients with resected IPs do not differ significantly in terms of age and sex compared to their NPS cohorts. Importantly, we found a low rate (5%) of incidental dysplasia and no carcinomas in IPS cases, perhaps alleviating some of the anxiety due to incomplete surveillance in these patients.

738  Gene Expression Profiling of Applicative Goblet Cell Carcinoid Tumors
Chelsea Mcelder, Daniel Gaston, Nourah M Obaid, Thomas Arnason, Karen Bedard, Wei-Yuarn Huang. Chelsea Mcelder, Daniel Gaston, Nourah M Obaid, Thomas Arnason, Karen Bedard, Wei-Yuarn Huang. Dalhousie University, Halifax, NS, Canada.
Background: Applicative goblet cell carcinoid (GCC) tumors exhibit a wide spectrum of tumor differentiation ranging from well-differentiated to poorly differentiated adenocarcinoma ex-GCC. The gene expression profile of GCCs remains relatively unknown. Our aim is to identify novel biomarkers that can distinguish subgroups of GCCs.
Design: A total of 10 GCCs were selected, including 2 well-differentiated (group A), 4 signet-ring carcinoma ex-GCC (group B) and 4 poorly differentiated adenocarcinoma ex-GCC (group C). Total RNA, isolated from formalin-fixed paraffin-embedded tissue samples, was used for RNA-sequencing analysis using Illumina HiSeq 2500. RNA-seq data was analyzed using a combination of HISA2 for alignment, featureCounts for gene level count estimation, and DESeq2 for differential expression analysis and quality control. Differential expression was estimated for all pairwise comparisons. Genes were considered to be differentially expressed if they had a >2-fold change in either direction and a Benjamini-Hochberg adjusted p-value < 0.05. Lists of differentially expressed genes were then used for enrichment analysis using the DAVID platform (version 6.8).
Results: Pairwise comparisons between tumor categories showed greater differences (by number of differentially expressed genes) between the A tumors and either the B or C tumors, which were more similar to each other (Table 1).

| Group Comparisons | # of Differentially Expressed Genes | % of Genes |
|-------------------|------------------------------------|-----------|
| A vs. B           | 2575                               | 3.1%      |
| A vs. C           | 2870                               | 10.8%     |
| B vs. C           | 40                                 | 0.07%     |

Both the A vs B and A vs C comparisons showed enrichment in a number of functional categories including translational initiation, elongation, and termination; nonsense-mediated decay; extracellular matrix organization and disassembly; focal adhesion; and basement membrane. Some of the most highly differentially expressed genes included those associated with ribosomes such as SNORD3A and RMRP (upregulated in A vs. C and C vs. A tumors) and several long intergenic non-coding RNAs. Uncharacterized RNA genes (LOC1001224734, LOC1001224734, LOC1001224734, LOC1001224734, LOC1001224734, LOC1001224734, LOC1001224734, LOC1001224734, LOC1001224734, LOC1001224734, LOC1001224734) were downregulated in C versus A tumors. Intriguingly, several olfactory receptor genes were also among the most strongly upregulated genes in the A compared to the C group.

Conclusions: This proof of concept study confirms differential gene expression between well-differentiated GCC and adenocarcinoma ex-GCC. This furthers our understanding of the GCC subgroups and their differing molecular characteristics.

739  Nuclear Exporter Protein CRM1/XPO1 a Novel Prognostic and Therapeutic Target in Gastric Cancer
Zaid Mahdi, Rahman Chaudhury, Irfana Muqbil, Amro Aboukameel, Rami Mohammad, Philip Philip, William Senapedis, Rafic Beydoun, Asfar Azmi. Wayne State University, School of Medicine, Detroit, MI; Wayne State University, School of Medicine, Detroit, MI; Wayne State University, School of Medicine, Detroit, MI; Wayne State University, School of Medicine, Detroit, MI.
Background: The high mortality rate associated with Gastric Cancer (GC) indicates the urgent need for identification of effective therapeutic markers. The nuclear exporter protein chromosome maintenance region 1 (CRM1) also known as exportin 1 (XPO1) is a nuclear-exclusive exporter of nuclear proteins. CRM1/XPO1 is often over-expressed in different solid tumors and hematological malignancies. Excessive nuclear export through CRM1/XPO1 over-expression results in unusual shuttling of different critical tumor suppressor proteins causing their functional inactivation.
Design: A detailed analysis on the correlation of CRM1/XPO1 with inflammation-metaplasia-dysplasia-carcinoma sequence progression was performed using immunohistochemistry in 70 cases: (1) Ten cases for normal gastric mucosa, (2) Ten cases for stomach with metaplasia with and without inflammation, (3) Ten cases for mucosa with low-grade dysplasia (4) Ten cases for mucosa with high-grade dysplasia, (5) Ten cases for gastric adenocarcinoma and (6) Twenty cases for metastatic gastric carcinoma. Positive correlations between the CRM1 staining and the clinicopathologic features as well as survival were analyzed. Gastric cancer cell lines were exposed to our recently developed specific inhibitors of nuclear export (SINE) and analyzed by cytotoxicity and molecular assays.
Results: CRM1/XPO1 was served as prognostic marker for poor outcome as positive expression rates of CRM1 in GC with aggressive behavior were observed. Targeting CRM1/XPO1 using SINE (Selinexor, KPT-185, KPT-8602) or telexipyrin (B<+c) resulted in inhibition of GC cellular growth (IC50 of 300 nM) induction of apoptosis (>50% apoptosis at IC50), doses and suppression of colony formation (p<0.01). Molecular analysis reveals nuclear retention of several important tumor suppressor proteins such HSP90 and FOXO3a, induction of pro-apoptotic proteins (Bax, PARP) and (rasp) 3 cleavage and suppression of pro-survival factor Bel-2. Selinexin, a CRM1 inhibitor was well tolerated in mice up to a dose of 15 mg/kg p.o. Pre-clinical efficacy trial of selinexin in sub-cutaneous xenograft of GC is ongoing.
Conclusions: Our findings strongly demonstrate the potential of CRM1/XPO1 to serve not only as a prognostic marker but also a therapeutic marker in GC that warrants further clinical investigations.

740  Differential Expression and Subcellular Localization of Tumor Suppressor Maspin in Adenocarcinoma of Gastroesophageal Junction and Its Precursors
Zaid Mahdi, Sijana Dzinic, Semir Vranic, Faruk Skenderi, Margarita Bernardo, Shijie Sheng, Rafic Beydoun, Wayne State University, School of Medicine, Detroit, MI; University Clinical Center of Sarajevo and School of Medicine, University of Sarajevo, Sarajevo, Bosnia and Herzegovina; Barbara Ann Karmanos Cancer Institute, Detroit, MI.
Background: The most important etiologic factor in the development of adenocarcinoma of the gastroesophageal junction (AdGEJ) is Barrett’s esophagus (BE). Difficulty regarding the diagnostic criteria of a number of cases of inflammation-metaplasia-low grade dysplasia (LGD)-high grade dysplasia (HGD)-AdGEJ sequence progression is mostly due to lack of reliable diagnostic markers. In contrast to tumor suppressor gene TP53 that is frequently mutated in AdGEJ hindering accurate diagnosis, an epithelial specific tumor suppressor maspin (Maspin) 1 neither mutated normally (2) nor mutated normally (albeit and spatiotemporally regulated) and 3) still remains the only endogenous inhibitor of histone deacetylase 1 (HDAC1). The purpose of this study is to investigate the role of maspin in the etiology of AdGEJ and its precursors.
Design: Maspin expression and subcellular localization were assessed in total of 50 cases of AdGEJ and its precursors using immunohistochemistry (clone G167-70; BD Biosciences). The normal GEJ mucosa was used as a control. Additionally, maspin was correlated with HDAC1 expression.
Results: Translocation of maspin from the nucleus to the cytosol was observed in all cases of intestinal metaplasia. Cytoplasmic localization was sustained in LGD and HGD. However, the expression and localization of maspin in AdGEJ was heterogeneous, ranging from high nuclear expression to complete maspin loss. There was no changes in HDAC1 expression or subcellular localization in AdGEJ precursors; however, HDAC1 expression was notably increased and inversely correlated with maspin expression in AdGEJ.
Conclusions: The early translational of maspin from the nucleus to the cytoplasm in intestinal metaplasia indicates the possible role of maspin in etiology of AdGEJ and its potential role in aiding pathologists’ to accurately diagnose BE due to sampling errors. Further studies are needed to correlate the observed heterogeneous maspin and HDAC1 expression in AdGEJ with patients’ prognosis.

741  The Role of Prolactin Receptor in Colonic Adenocarcinoma and Its Precursors
Zaid Mahdi, Kerri Ann Latchmining, Rafic Beydoun, Hayan Jaralbi, Wayne State University, School of Medicine, Detroit, MI.
Background: Prolactin receptor (PR) is the cognate receptor of prolactin hormone that has the ability to bind and activate, often the intracellular Janus Kinase signaling pathway, leading to cell growth. Besides its known role in the tumorigenesis of breast, endometrial and cervical cancers, previous clinical data shows PR to be expressed in colorectal carcinoma (CRC). The aim of this study was to evaluate the level of expression of PR in precancerous conditions of CRC to better understand the main role of the hormone and its receptor in the initiation and/or the progression of CRC.
Design: We investigated a total of 50 cases of surgically resected polypectomies and colorectal resections, comparing normal colorectal mucosa with normal and abnormal colorectal mucosa.

Results: All specimens were included in this study, and 28 cases were polyps (9 high-grade dysplasia and 19 adenomas), 10 cases were adenomas (n=6; low-grade dysplasia and n=4; intermediate-grade dysplasia), 5 cases were carcinomas, and 5 cases were other benign tumors. Immunohistochemical staining for CDX2 was performed using monoclonal CDX2 antibody (Ab-1, Clone B6.2) and was scored for extent, intensity, and cellular location (membranous, cytoplasmic or both).

Conclusions: Our data reveals a large area of incidental findings in the routine appendectomy specimens, which included inflammatory conditions, and various benign as well as malignant neoplasms. This highlights the importance of thorough microscopic examination of all appendectomy specimens to identify unsuspected conditions, which otherwise might go undiagnosed.

742 PD-L1 Expression in Post-Transplant Lymphoproliferative Disorder (PTLD) After Small Bowel Transplant

As well as malignant neoplasms. This highlights the importance of thorough microscopic appendectomy specimens, which included inflammatory conditions, and various benign neoplasms.

Conclusions: Our data reveals a large area of incidental findings in the routine appendectomy specimens, which included inflammatory conditions, and various benign as well as malignant neoplasms. This highlights the importance of thorough microscopic examination of all appendectomy specimens to identify unsuspected conditions, which otherwise might go undiagnosed.

744 MSH3 and EMAST in Inflammatory Bowel Disease-Associated Dysplasia and Carcinoma

Alexander Mario, Frank Reverta, Chanjuan Shi. Vanderbilt University Medical Center, Nashville, TN.

Background: Inflammatory bowel disease (IBD) increases risk of colorectal cancer (CRC) through an inflammation-dysplasia-carcinoma sequence. Elevated microsatellite alterations at selected tetranucleotide repeats (EMAST) in CRCs is thought to be a form of microsatellite instability that is initiated by inflammation and involved in CRC progression. Dysfunction in MSH3, a mismatch repair protein, may lead to EMAST in CRCs. Shifting of MSH3 from the nucleus to the cytoplasm may be one of the mechanisms underlying MSH3 deficiency. In this study, we explored the role of MSH3 and EMAST in inflammatory bowel disease-associated dysplasia and carcinoma.

Design: 24 FFPE blocks from IBD colectomies had inflammation (n=20), low grade dysplasia (LGD; n=20), high grade dysplasia (HGD; n=6), and CRC (n=7). Seven additional IBD-associated CRCs were included from tissue microarrays. MSH3 expression was evaluated by immunohistochemistry (IHC). The location (nucleus versus cytoplasm) of MSH3 labeling was recorded. IHC scores of the nuclear labeling were obtained based on staining intensity and percent: negative=0, weak=1, moderate=2, and strong=3; 0-4%:1, 5-24%:2, 25-74%:3, and 75-100%:4. DNA was isolated from five IBD-associated CRCs and one normal colon epithelial cell line for EMAST.

Results: Weak (n=15), 75% (n=5), 25% (n=1) nuclear MSH3 labeling was detected in inflammatory colon mucosa, mostly restricted to the deep crypts. Dysplasia was associated with an increase in staining intensity and/or percent. Fifteen of (20 (75%) LGD and 5 of 6 (83%) HGD lesions had moderate-to-strong nuclear labeling, which was more prominent in the deep crypts. Most CRC’s had moderate-to-strong labeling, whereas two showed weak-to-moderate staining at the tumor surface while deeper, invasive glands clearly showed weaker nuclear staining and positive cytoplasmic staining. There was statistically significant increase in MSH3 expression in LGD (mean IHC score=7.3), HGD (mean=8.5), and CRC (mean=9.2) compared to inflammation without neoplasia (mean=3.7; p<0.01). PCR analysis of 5 CRCs showed no EMAST, including one with decreased nuclear MSH3 expression.

Conclusions: Altered MSH3 expression is present in IBD-associated dysplasia and invasive carcinoma, with most of the cases showing increased nuclear expression and a few cases with decreased nuclear and increased cytoplasmic expression in invasive carcinoma. Unlike sporadic CRCs, where about 60% of cancers have EMAST, MSH3 may be in IBD-associated CRCs.
Conclusions: AURKA expression is often increased in tumors with high-risk features but seems to be decreased after treatment with imatinib. Therefore targeting AURKA with pharmacologic inhibitors may have limited utility in patients who have received imatinib.

746 Two-Stain Rather Than Four-Stain Immunohistochemical Screening in Colorectal Cancer May Fail to DetectMismatch Repair Deficiency
Michael Markow, Rachel Pearlman, Christina A Arnold, Deborah Knight, Heather Hampel, Wendy L Frankel. The Ohio State University Wexner Medical Center and Comprehensive Cancer Center, Columbus, OH.

Background: Universal tumor screening for Lynch syndrome (LS) in colorectal cancer (CRC) is recommended, and immunohistochemistry (IHC) for the mismatch repair (MMR) proteins (MLH1, MSH2, MSH6, PMS2) is a common method. The MMR proteins dimerize to form heterodimer complexes. If MSH2 is mutated, MSH2 binds with MSH1, resulting in sole absence of MSH1. If MSH2 is mutated, both MSH2 and MSH6 should be absent. MLH1 and PMS2 act in similar fashion. To reduce costs, some screen using only MSH6 and PMS2, with reflex to the partner stain if either are absent (two-stain method). We analyzed tumors with any MSH6 expression but absent MSH2 to determine if the two-stain method could miss MSH2 mutations.

Design: 1,300 CRC patients enrolled in the Ohio Colon Cancer Prevention Initiative underwent universal tumor screening with microsatellite instability testing and IHC. MSH2 and MSH6 stains were reviewed for proportion of positive cells and intensity of staining relative to control. A score of 1 to 5 was assigned. Absent staining was considered absent. Staining intensity was graded as: 1, less than control with ambiguous nuclear staining; 2, minimally less than control but with convincing nuclear staining; 3, equal to or greater than control. For patients with MMR deficiency, next-generation sequencing (NGS) of germline DNA for MMR genes was done (Coloseq, University of Washington). If germline was negative, NGS was done on tumor DNA to assess for double somatic mutations.

Results: Twelve patients (0.9%, 12/1300) had absent MSH2 expression but weak MSH6 expression. Ten had LS due to pathogenic mutations in MLH2: five with grade 2 intensity and 30% of cells staining for MSH2, five with grade 1 MSH6 and 5-25% staining. Two had negative germline testing and double somatic mutations in MSH2: one with grade 1 intensity and 5% staining, one with grade 2 intensity and 30% staining. A thirteen case with absent MSH2 was grade 3 with 30% of cells staining for MSH6, germline NGS is pending.

Conclusions: The two-stain method can miss patients with MSH2 mutations when screening for LS. Convincing staining that is somewhat weaker than the control is difficult to evaluate and may be interpreted as present. Weak MSH6 expression can be retained in the absence of functional or antigenically intact MSH2, whether by forming an undiscovered heterodimer or through other means. If one uses the two-stain method, weak MSH6 staining should trigger reflex to MSH2 with consideration of MSI testing to identify a greater number of patients with LS.

747 Expression of Immunoregulators IDO1, and PD-L1 in Gastrointestinal Stromal Tumors
Andres Matoso, Ayesha Siddiquie, Kara A Lombardo, Murray B Resnick, Ross Taliao, Li/J Wang. Brown University, Providence, RI.

Background: Immune microenvironment is emerging as an important prognostic factor with potential therapeutic targets for various malignancies. Although the immunoregulators programmed death-ligand 1 (PD-L1) and indoleamine 2,3-dioxygenase (IDO1) have been studied in some tumor types, the significance of the immunosuppressive stromal regulators (IDOs) is largely unknown.

Methods: Tissue microarrays were constructed from 131 GISTs from our pathology files between 3/1996 to 3/2016. Immunohistochemistry for IDO1, and PD-L1 was performed. At least 10% of positive cells with moderate intensity staining was considered positive. Results were correlated with size, mitoses, and clinical followup. Tumor infiltrating lymphocytes (TIL) were counted using an image analysis software and reported in number of cells/mm².

Results: The mean age was 62 years (range 30-89) including 67 males and 64 females. The average size was 5.6±4.5 cm and the average mitotic count was 7.2±50.4IPP. The tumor location included: 89 (68%) stomach (including 6 SDH deficient), 34 (26%) small intestine, 3 (2.2%) abdominal wall, 2 (1.5%) rectum, 2 (1.5%) colon and 1 (0.8%) esophagus. The mean follow up was 63 months. Nineteen (14.5%) were malignant. Metastatic sites included mesentery (n=8), liver (n=6), lymph nodes (n=3), fallopian ligament (n=1), and retroperitoneum (n=1). Five patients died of disease with an average survival of 61 months (range 7-127). IDO1 was positive in 116 (89%), including 14/19 (78%) malignant and 102/112 (91%) of benign tumors (p=0.07). PD-L1 was positive in 89 (68%), including 11/19 (58%) malignant and 78/112 (70%) benign tumors (p=0.4). PD-L1 positive tumors had a larger average size (6.3±4.4 vs. 4.4±3.3; p=0.02) and higher number of mitoses/50HPF (8.9±5.4 vs. 3±3.5; p=0.006) than PD-L1 negative tumors. There was no significant difference in size or mitotic count between IDO1 positive and negative tumors. The average number of CD8-positive TILs was 168±35/ mm² in PD-L1 and 153-30% of cells staining for MSH2 and MSH6. PD-L1 positive tumors with staining of MSH2 cells had significantly higher numbers of PD-L1 positive TILs than PD-L1 negative tumors (113±21 vs. 104±18; p=0.001).

Conclusions: The majority of GISTs express PD-L1 and IDO1. Expression of PD-L1 and IDO1 was associated with increased tumor size and higher mitotic activity. PD-L1 and IDO1 could play a significant role in the tumor biology of GISTs, and immunotherapy targeting one or both may provide novel treatment options.

750 EPB41L5 and PKD2 Are Biomarkers of Metastasis in Pancreatic Neuroendocrine Tumors
Tania Mendoza, Steven J Eschrich, Kevin Neil, Jonathan R Stroburg, Nazir Asjad, Damir Cojocanovic. H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Eli Lilly and Company, Indianapolis, IN.

Background: The malignant behavior of pancreatic neuroendocrine tumors (PNETs) is currently unpredictable. PNETs are indolent but have malignant potential if left untreated. Unfavorable prognosis and limited surgical options when PNETs metastasize to the liver. Increased tumor burden in the liver is common cause of death in PNET patients. Molecular biomarkers predicting metastasis in PNETs are needed to improve treatment selection.
were significantly more likely to have advanced neoplasia on follow-up colonoscopy (p=0.04, HR=2.3, 95% CI 1.03-8.31). When patients with previous advanced neoplasia were excluded from analysis, patients with TVASF were still significantly more likely to have advanced neoplasia on follow-up (p=0.02, HR=2.7, 95% CI 1.29-11.70).

**Conclusions:** TVASF are frequently associated with prior and subsequent advanced neoplasia. Patients with TVASF may require more aggressive colonoscopic follow-up, but further longterm studies are necessary.

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**751 Loss of YAP-1 Expression in Gastrointestinal Neuroendocrine Carcinomas**

James A Miller, Tamara I Loaton. Johns Hopkins, Baltimore, MD.

**Background:** The Hippo pathway is involved in regulation of organ size and includes the Hippo and Warts phosphorylases, and the transcriptional co-activator, Yorip (YAP). YAP signaling is upregulated in many cancers and correlated with poor outcomes. We developed a gene expression signature to distinguish gastrointestinal neuroendocrine carcinoma and adenocarcinoma. We now report that loss of YAP1 gene expression is common in lung and prostatic neuroendocrine carcinoma. We tested whether immunohistochemistry for this marker might be useful in gastrointestinal neuroendocrine carcinomas.

**Design:** Ten tissue microarrays of gastrointestinal neuroendocrine carcinomas, including 111 unique cases, were stained for YAP1, synaptophysin, and chromogranin. YAP1 staining was considered positive if cytoplasmic or nuclear staining was observed in the tumor cells on any tumor core, and YAP1 was interpreted as negative if no cytoplasmic or nuclear staining was seen in tumor cells on any tumor core in the presence of adequate stromal/endothelial staining. Synaptophysin and chromogranin were interpreted as positive if any cytoplasmic staining was seen on any tissue core, while they were interpreted as negative if no cytoplasmic staining was seen in tumor cells on any tumor core.

**Results:** One hundred seven (96.4%) of the cases had documented metastasis, 2 (1.8%) were solitary tumors, and the presence of metastases could not be determined in 2 (1.8%) cases. Fifty two (46.8%) primary tumors, and 100 (90.0%) metastases were examined (with both sites examined in 41 cases). Primary sites included pancreas (46, 47%), liver (4, 4%), small bowel (37, 38%), colon (8, 8%), and stomach (2, 2%). Metastases included liver (105, 98.1%), soft tissue (2, 2%), lymph nodes (1, 0.9%), ovary (1, 0.9%), and not-specified (2, 2%). YAP1 was lost in 47 (42%) of cases and was retained in 64 (58%) of cases. YAP1 was lost in 21 (40.4%) of the 52 primaries, and retained in 31 (59.6%) of the 52 primaries. Synaptophysin was positive in 47 (47%) of the 100 metastases and retained in 53 (53%) metastases. Synaptophysin was positive in 109 (95.5%) of cases, and negative in 1 (0.9%) case. YAP1 staining was available in both the primary and metastasis in 41 cases. Chromogranin was positive in 106 (98.1%) cases, and negative in 4 (4%) cases.

**Conclusions:** Loss of YAP-1 is strongly associated with gastrointestinal neuroendocrine carcinomas. Future studies need to determine if there is a relationship between YAP-1 loss and neuroendocrine differentiation, as well as the association with prognosis may be of interest.

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**752 Tubulovillous Adenomas with Serrated Features Are Associated with a Higher Risk of Advanced Neoplasia on Follow-up**

Mohamed Mostafa, Christopher Hartery, Catherine Hagen. Mayo Clinic, Rochester, MN.

**Background:** Tubulovillous adenomas (TVA) and traditional adenomas (TSA) represent precursor lesions for two discrete pathways of colorectal carcinogenesis. Occasionally, TVA show focal features resembling TSA. Currently, the biological roles of TVA and degree of neoplasia was recorded via chart review. Advanced neoplasia on prior or baseline colonoscopy was present in 16.5%, p<0.01). Patients with TVA showed a trend of having more synchronous tubular adenomas (43.3% vs. 25%, p=0.06). 70 patients had at least one previous polyp and 94 patients had at least one follow-up colonoscopy. Patients with TVASF were significantly older (70.0 vs. 64.4, p<0.007) and were more likely to have had a prior endoscopic diagnosis of polyps (33.3% vs. 14.0%, p=0.013) Patients with TVASF were significantly more likely to have advanced neoplasia on follow-up colonoscopy.

**Design:** Five primary PNET from 5 patients (mean age 66; 3M/2F), 6 primary PNET with a higher risk of advanced neoplasia on follow-up colonoscopy (M-PNET), and 6 PNET metastatic to liver (ML-PNET) from the same six patients were selected. RNA extracted from these frozen samples was analyzed on Affymetrix U133 2.0 gene chip.

**Results:** 751 Loss of YAP-1 Expression in Gastrointestinal Neuroendocrine Carcinomas

**Background:** The Hippo pathway is involved in regulation of organ size and includes the Hippo and Warts phosphorylases, and the transcriptional co-activator, Yorip (YAP). YAP signaling is upregulated in many cancers and correlated with poor outcomes. We developed a gene expression signature to distinguish gastrointestinal neuroendocrine carcinoma and adenocarcinoma. We now report that loss of YAP1 gene expression is common in lung and prostatic neuroendocrine carcinoma. We tested whether immunohistochemistry for this marker might be useful in gastrointestinal neuroendocrine carcinomas.

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**Results:** One hundred seven (96.4%) of the cases had documented metastasis, 2 (1.8%) were solitary tumors, and the presence of metastases could not be determined in 2 (1.8%) cases. Fifty two (46.8%) primary tumors, and 100 (90.0%) metastases were examined (with both sites examined in 41 cases). Primary sites included pancreas (46, 47%), liver (4, 4%), small bowel (37, 38%), colon (8, 8%), and stomach (2, 2%). Metastases included liver (105, 98.1%), soft tissue (2, 2%), lymph nodes (1, 0.9%), ovary (1, 0.9%), and not-specified (2, 2%). YAP1 was lost in 47 (42%) of cases and was retained in 64 (58%) of cases. YAP1 was lost in 21 (40.4%) of the 52 primaries, and retained in 31 (59.6%) of the 52 primaries. Synaptophysin was positive in 47 (47%) of the 100 metastases and retained in 53 (53%) metastases. Synaptophysin was positive in 109 (95.5%) of cases, and negative in 1 (0.9%) case. YAP1 staining was available in both the primary and metastasis in 41 cases. Chromogranin was positive in 106 (98.1%) cases, and negative in 4 (4%) cases.

**Conclusions:** Loss of YAP-1 is strongly associated with gastrointestinal neuroendocrine carcinomas. Future studies need to determine if there is a relationship between YAP-1 loss and neuroendocrine differentiation, as well as the association with prognosis may be of interest.

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**EBV and Microsatellite Instability Can Occur in a Subset of Lymphocyte-Rich Intrahepatic Cholangiocarcinomas**

Tatjana Monadjem, Hee Enn Lee, Tung-Teh Wu. Mayo Clinic, Rochester, MN.

**Background:** Characteristics of lymphocyte-rich cholangiocarcinoma (LRICC) have not been well described. Lymphocyte-rich carcinoma in gastrointestinal tract has been associated with EBV and/or microsatellite instability (MSI). However, such association in cholangiocarcinoma (ICC) has not been studied in detail. We aimed to evaluate clinicopathologic characteristics of LRICC and its EBV and MSI status.

**Design:** The density of tumor infiltrating lymphocytes (TIL) was graded in 154 ICCs (0 = 0, 1 = 1-5 TIL/HFP (n=114), 1 = 6-10 TIL/HFP (n=6), 2 = 11-15 TIL/HFP (n=18), 3 = 16-21 TIL/HFP (n=16)); cases with 3 + 0 were selected and LRICC and lymphocyte-poor ICC (LPICC, respectively. Fifteen LRICC were compared to the same number of randomly selected LPICCs. EBV in situ hybridization and immunostains for MLH1, PMS2, and MSI2 were performed. Cases were classified into proficient mismatch repair (pMMR), MSI-L, MSI-H, and deficient MMR (dMMR). Clinical data were correlated with EBV and MMR status, and with pathologic features.

**Results:** Median age of the LRICC and LPICC group was 59 years (range 31-83 years) and 67 years (range 35-74 years), respectively. Histologic type was adenocarcinoma (61%) in all cases except one carcinosarcoma (LRICC group) and one combined hepatocellular carcinoma and ICC (LPICC group). Two LRICCs and 3 LPICCs showed low histologic grade (LG) and remaining cases high grade (HG) ADCA. Tumor AJCC stage of the LRICC group was T1 (n=9), T2 (n=6), T3 (n=2), N0 (n=7), N1 (n=3), and N2 (n=2), compared to T1 (n=1), T2 (n=6), T3 (n=1), N0 (n=1) and N2 (n=1) and N3 (n=4) in LPICC group. Two LRICCs showed distant metastasis compared to none in the LPICC group. The LRICC group tended to have a longer disease-free survival than the LPICC (mean = 12.4 vs. 10.6 years, p=0.007). Two (13.3%) LRICCs (HG ADCA with pMMR and T1N1M1) had a trend of EBV-positivity, but further longterm studies are necessary.

**Conclusions:** EBV-positivity is associated with a higher Risk of Advanced Neoplasia on Follow-up.

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**ANNUAL MEETING ABSTRACTS**

**All Patients With Prior Follow-Up**

**Patients With Prior Advanced Neoplasia Excluded**

(188A)
Conclusions: Our findings indicate that EBV infection and MSI may play a role in carcinogenesis of intraductal cholangiocarcinoma, in particular in a subset of lymphocyte-rich tumors.

Table:

| Age, F/M | Distinguishing clinical features | More specific imaging findings | Endoscopic findings | 5y survival (%) |
|----------|---------------------------------|-------------------------------|-------------------|---------------|
| 66, 0.7 | Similar to PC with duct dilatation (mean, 5.3mm) and parenchymal atrophy (mean, 12.2mm of the body) | Non-exposed position (without a central dimple, or ulceration) (n=7) | 45 |
| 59, 1.1 | Younger patients. *Common pain (53%, vs 29%). *Less jaundice (53%, vs 85%). *Lowest pre-op hemoglobin (mean, 9.6mg/dl, vs 11.6). | Overt white granular tumors on the duodenal mucosa surrounding the papilla. (n=7) | 41 |
| 63, 0.6 | *Commonly associated with cholangitis (39%, vs 9%) and pancreatitis (21%, vs 3%). *Minimal weight loss (BMI=25%; 92%, vs 55%). | *Most lacked pancreatic duct dilatation (mean, 2.8mm). *Swollen intact mucosa, with spherocytosis causing white small nodular granular lesion. (n=4) | 64 |

Mixed NOS (n=41, 38%)
Non-specific other than pancreatic cysts >1cm only in this subtype (n=6, 15%)

Pre-operative diagnosis Pathological findings

| | AC (%) | PAC (%) | PC/BC (%) | Duodenal (%) | Size of overall tumor/ins. (cm) | LVI/PNI (%) | LN mets (%) |
|----------|--------|-------|--------|------------|-----------------|-----------|------------|
| Ampullary-ductal | 39 27 24 3 | 1.8±1.7 | 73±6 | 61 |
| (P)ampullary- ductal | 26 16 21 37 | 4.8±2.8 | 47±42 | 53 |
| Intra-ampullary tubular adenoma-associated | 71 7 22 0 | 2.3±0.9 | 36±31 | 36 |

Conclusion: The 4 site-based categories of ampullary carcinomas recognized in the CAP protocol have distinctive imaging and clinical characteristics in addition to specific pathologic features and biologic behavior.

Loss of Expression of CDX2 Is Not a Useful Method for Detecting Epigenetic Gene Alterations

Eva Musulen, Anna Martinez-Caruso, Sebastian Moran, Aurelio Ariza, Miguel Angel Carrasco, Manel Esteller. Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain; Hospital Universitari General de Catalunya, Sant Cugat del Valles, Barcelona, Spain; Bellvitge Biomedical Research Institute (IDIBELL), L’Hospitalet del Llobregat, Barcelona, Spain.

Background: Transcriptional factor CDX2 is a major regulator of gut development and involved in colorectal cancer (CRC) as a suppressor gene. Lack of expression of CDX2 has recently been described in 4.1% of CRC and identifies among Stage II and III CRC a subgroup with worse prognosis. Herein, we analyze CDX2 immunohistochemical (IHC) expression and CDX2 methylation in different series of CRC to correlate the results with molecular profiles and prognosis.

Design: A TMA from 36 FFPE MSI-H MLH1(-)/Braf-mut CRC was analyzed by IHC with anti-CDX2 mouse monoclonal antibody (Dako Agilent Technologies). Additionally, epigenetic analysis of 123 CRC was performed using Infinium 450K beadchip (Illumina). CDX2 was considered as methylated when average β-value in Cpg island of promoter zone was over 50%. In 14 CRC both IHC and epigenetic analysis was performed. Clinical, molecular, and histopathologic parameters were established and statistically correlated.

Results: Ten of 36 (28%) MLH1(-)/Braf-mut cases were CDX2(-). Lack of CDX2 expression correlated with CDX2 methylation, despite some CDX2 methylated cases retain CDX2 stain (12 IHC(-)/9 CDX2-Met). Regarding methylation, 55% were CDX2 methylated, being 41% in MSS and 83% in MSI-H samples. CDX2 methylation was more frequent in MSI-H and mesenchimal-like phenotype groups (5/6 cases). Despite there was no correlation with any histopathologic parameter analyzed, in MSS group, p53 wt tumors showed higher methylation levels than those with p53-mut (U Mann-Whitney test; p=0.008). We observed a statistical significant association between CDX2 methylation with shorter relapse free survival in a set of patients of patients of whole cohort with clinical survival data available (N = 44; Log Rank P=0.02).

Conclusion: Although in our set lack of CDX2 expression corresponds to CDX2 methylated samples, this mechanism is also related to cases with expression of CDX2. Our results suggest an enrichment of CDX2 silencing not only in MSI-H and mesenchiral-like cases, but also in MSS p53-wt tumors. Despite CDX2 methylation could be relevant as a prognostic factor in CRC, further studies are necessary to elucidate the relationship with protein expression by IHC and, consequently, its clinical impact.

Clinical Manifetations of Pathologic Site-Based Classification of Ampullary Carcinomas (ACs): An Analysis of 107 Resected ACs Demonstrates Distinct Clinicopathologic Associations

Takashi Muraki, Michelle D Reid, Steven Kellin, Serdar Balci, Nobuyuki Ohike, Takuma Tajiri, Yue Xue, Bahar Memis, Aarti Sekhar, Pardeep Mittal, Alyssa Krasinskas, David Kooby, Shishir Maithel, Juan M Sarmiento, Volkan Adsay, Eva Musulen, William R Taylor, Tracy C Yab, Douglas W Mahoney, John B Kisiel, Karim J Kassam, Teresa Whitfield, David J Cohn, Thomas Smyrk, Mayo Clinic, Rochester, MN.

Background: Verrucous Carcinoma of the Esophagus shares a Methylation Profile with Intraductal Squamous Carcinoma

Prasuna Shugap, William R Taylor, Tracy C Yab, Douglas W Mahoney, John B Kisiel, David A Abiguit, Thomas Smyrk. Mayo Clinic, Rochester, MN.

Conclusions: Our findings indicate that EBV infection and MSI may play a role in carcinogenesis of intraductal cholangiocarcinoma, in particular in a subset of lymphocyte-rich tumors.

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Conclusions: Our findings indicate that EBV infection and MSI may play a role in carcinogenesis of intraductal cholangiocarcinoma, in particular in a subset of lymphocyte-rich tumors.
758 Characterization of Lgr5 Expression in Colorectal Neuroendocrine Tumors
Tomoyuki Nakajima, Takashi Uehara, Yasuhito Maruyama, Yukihiko Kobayashi, Hiroyoshi Ota, Takayuki Honda. Shinshu University School of Medicine, Matsumoto, Japan.
Background: Lgr5 is a positive-feedback regulator of crypt stem cells, and loss of Lgr5 expression is associated with colorectal cancer (CRC). We hypothesized that the expression of Lgr5 is an early event in colorectal cancer.

Methods: We performed qPCR analysis of Lgr5 expression in normal colorectal mucosa, adenomatous polyps (not containing invasive cancers), adenocarcinomas (Stage T1N0M0 and T2N0M0), and carcinoids. We defined adenomas as a polypic tumor of the colon that consists of only glandular tissue and contains no sign of invasion. We categorized tumors as adenomas or carcinoids (adenoma ex carcinoid). We performed immunohistochemical staining to evaluate the expression of Lgr5.

Results: We found that Lgr5 expression levels were significantly higher in adenomas and carcinoids compared to normal mucosa and adenomatous polyps. In adenomas, the expression of Lgr5 was highest in the superficial epithelial layer and gradually decreased towards the crypt base. In carcinoids, Lgr5 expression was also high in the superficial epithelial layer, but the expression was more uniform throughout the tumor.

Conclusions: Our results suggest that Lgr5 expression is an early and important event in the development of colorectal cancer. Further studies are needed to understand the role of Lgr5 in colorectal cancer progression.

760 Using Pathology Reports to Assess the Endoscopist’s Catch and Pathologist’s Call in a Series of 11,456 Large Bowel Polyp Specimens with a Focus on Serrated Polyps
Anjana Naiky, Jennifer M Dometrich, Michael Bonert. McMaster University, Hamilton, ON, Canada.
Background: Variations in polyp acquisition and interpretation are not routinely assessed using clinical data, and may give insight into modifiable factors that influence detection and prevention of colorectal cancer (CRC). Observational data is commonly analyzed using descriptive statistics or regression analysis in other sectors.

Design: Surgical pathology reports for a 3 year period, in an academic centre, were data-mined using a custom computer program that extracted all large bowel polyp specimens and their diagnostic information using keyword searches, a fuzzy matching algorithm, and rule-based pruning. The dataset was compared to pathologist reads for a random subset of reports to assess accuracy.

Results: Computer based categorization was successful in 99% of cases. An audit of 200 cases revealed that the algorithm accurately categorized 99% of cases. The pathologists’ and endoscopists’ Sessile Serrated adenoma (SSA) rates were uniformly lower than the pathologists’ and endoscopists’ Hyperplastic polyp (HP) rates, with HP rates of median/stdev/max/min for pathologists were 20.3%, 20.4%, 4.6%, 27.3%, 13.1% and 2.4%, 9.3%, 0.4%, respectively.

Conclusions: Pathologists could be separated into two groups based on the SSA rate. Pathologists with higher SSA rates may have different diagnostic criteria or differentiating abilities.

761 Gastrointestinal and Pancreatic Findings in Patients with McCune-Albright Syndrome
Michaël Noël, Laura D Wood, Wenzel Hackeng, Lodewijk A B Brossen, Feryll Bhalje, Marjia Deheshki, Jun Yu, Alison Boyce, Corine Robinson, James E Eshleman, Ralph H Hruban, Michael G Goggins, Michael T Collins, Anne Marie Lennon, Elizabeth A Moon. Johns Hopkins University, Baltimore, MD, United States.
Background: McCune-Albright Syndrome (MAS) is a sporadic syndrome, caused by somatic (post-zygotic), activating mutations in the GNAS1 gene. MAS patients have a clinical triad of skeletal, endocrine and dermatological abnormalities including fibrous dysplasia of bone, precocious puberty, and cafe-au-lait spots. The same GNAS mutation in codon 201 has been reported in several gastrointestinal, pancreatic and other tumor types.

Design: We report the findings from upper endoscopic and imaging examination of 7 patients with MAS and pancreatic findings in 2. A variety of polyps and lesions was found throughout the esophagus, stomach, small intestine and pancreas. Lesions were biopsied/resected and submitted for histopathological evaluation and GNAS1 mutation analysis by pyrosequencing the FFPE tissues.

Results: All seven patients had heterotropic gastric mucosa (polypoid mucosa with oxyntic and/or foveolar type epithelium, outside of GNAS), with GNAS1 mutations in 12/17 lesions. Gastric hyperplastic-type polyps were present in 5/7 patients (2.5 GNAS1 mutated), while fundic gland polyps arose in 2/7 patients (both GNAS1 wild type). One patient had a Peutz-Jeghers-like polyp (GNAS1 wild type) of the ampulla of Vater, but with less smooth muscle proliferation and more inflammation. One patient had intestinal metaplasia at the gastroesophageal junction. All patients had EUS findings suggestive of focal parypillary mucinous neoplasm (IPMN), but only 2 underwent surgical intervention. Resection confirmed the IPMN diagnosis in 2/2 GNAS1 mutated in both patients and revealed a small duodenal proliferation of neuroendocrine cells (GNAS1 wild type), bordering on a well-differentiated neuroendocrine tumor, in one patient. Two patients had high-grade dysplasia (HGD); in: an IPMN polyp and in a hyperplastic polyp. In all but 1 analyzed sample, the adjacent normal tissue was GNAS1 wild type.

Conclusions: We described the pathological spectrum of gastrointestinal and pancreatic lesions in patients with MAS. We found enrichment for lesions known to have GNAS1 mutations (IPMNs, gastric heterotopia, gastric adenomas with oxyntic differentiation). Finding HGD in 2 patients raises the possibility of an increased risk for malignant transformation.

762 A Study of Appendiceal Crypt Cell Adenocarcinoma (So-Called Goblet Cell Carcinoid and Its Related Adenocarcinoma)
Dipti N V Konaka, Deepak S Government, Angela Lamass, Paul Fulford, Juan Valle, Bipasha Chakrabarty. The Christie Hospital, Manchester, United Kingdom; The University of Manchester, Manchester, United Kingdom.
Background: Goblet cell carcinoids (GCCs) of appendix are rare tumors, characterized by a carcinoid-like organoid growth pattern of nests and glands, and predominant cellular component is generally mucinous cells with goblet/signet-ring morphology. Despite the term carcinoid, endocrine features are inconspicuous, and its behavior is distinct from carcinoid. Its high grade counterpart is designated as adenocarcinoma ex goblet cell carcinoid (AEGCC). We conducted a retrospective study of 105 GCCs/AEGCCs to find prognostic values of a variety of clinico-pathologic features.

Design: The tumors were subclassified as low grade (LG), equivalent to classic type (Tang A), and high grade (HG), corresponding to high grade neuroendocrine tumor (HGNET). Correlation of clinicopathological parameters was performed using Pearson’s correlation coefficient. The following were investigated: age, gender, stage, size, perineural, vascular and lymphovascular invasion, nuclear grade (low vs. high), histological HG component (%) mucinous cell (%), neuroendocrine (%), extracellular mucin (%), type of surgery, resection margin, and chemotherapy.

Results: Age at diagnosis ranged 25-70years (median, 54), with M:F=1:0.94. 35 tumors were pure LG while the remaining contained variable HG component ranging 1-95%.
763 Detection of Anaplastic Lymphoma Kinase (ALK) Rearrangement in Colorectal Cancer: An Immunohistochemical Study of 128 Cases

Sahar Nozad, Sungeun Kim, Christin E Sheehan, David M Jones, Jeffrey Ross. Albany Med Coll, Albany, NY.

Background: Discovery of anaplastic lymphoma kinase (ALK) gene rearrangement in a subset of lung adenocarcinomas has led to a standard of practice with targeted therapy. Immunohistochemistry (IHC) has been approved as a screening tool to identify ALK rearrangement in lung cancer. ALK rearrangement appears to be very rare in colorectal cancer (CRC). We tested the utility of ALK IHC as a screening tool to detect ALK rearrangement in CRCs of variable molecular pathways.

Design: Archived pathology materials from 71 randomly selected CRCs, 19 mismatch repair (MMR) deficient CRCs, 38 sessile serrated polyp (SSP)-associated lesions (25 SSP, 3 SSP with high grade dysplasia, 14 SSP associated CRCs) were retrieved and reviewed. An index case CRC with ALK rearrangement confirmed by advanced molecular technique and fluorescent in situ hybridization (FISH) served as a known positive. Representative sections from paraffin-embedded formalin-fixed tissue blocks were used for both immunohistochemical staining for ALK (D5F3E7, Cell Signaling/Ventana) and fluorescent in situ hybridization (FISH) (46D5, Vysis). IHC was scored semiquantitatively. A cutoff score of 2+ was used to define ALK positivity.

Results: Twelve (9%) of CRCs showed focal weak cytoplasmic staining for ALK, comparable to the intensity and extent of ALK immunoreactivity in the index case as follows: 5 (7%) random, 5 (26%) MMR deficient, and 2 (20%) SSP-associated/MMR proficient CRCs. The index case was MMR proficient, right sided colon cancer with marked intratumoral morphologic heterogeneity. The intensity or extent of ALK protein expression did not differ with increased incubation time.

Conclusions: A subset of CRCs are ALK positive by IHC, similar to a known ALK rearranged CRC. ALK IHC positivity is more frequent in MMR deficient CRC, suggestive of a role of high mutational load in ALK expression. IHC may potentially be used as a screening tool for detection of ALK rearrangement in CRCs of variable molecular pathways. Comprehensive genomic profiling of the ALK IHC-positive cases in this study set is warranted.

764 Co-Expression of HER Family Relates to Progression and Lymph Node Metastases in Human Colorectal Cancer

Hiroyuki Nozaka, Ai Igarashi, Miku Togashi, Sayaka Kurosawa, Yayoi Takahashi, Hiroyuki Nozad, Sahar Nozad, Sungeun Kim, Hwajeong Lee, Christine E Sheehan, David M Jones, Jeffrey Ross. Albany Med Coll, Albany, NY.

Background: Cancerous development is often associated with genetic alternation or mutation, and it is reported that the carcinogenesis of colon and rectum is caused by accumulation of genetic lesions. Here, the authors analyzed if expression of HER family is related with the progression of colorectal cancer.

Methods: 1) qRT-PCR analysis : expression rate of HER2, HER3 and HER4 was measured and compared with no loss of expression in the controls (p=0.005, Fisher’s exact test). Of the cases with loss of MMR protein expression, 100% (5 of 5 cases) had loss of MLH1 and MSH2 expression and one additionally had a loss of MSH2 and MSH6 expression.

Results: Conclusions: This study demonstrates that HER family is potentially a new molecular target in colorectal cancer therapy. However, this study does not provide important prognostic information, and % of HG component should be additionally detected in future studies.

765 The Frequency and Patterns of MMR Protein-Deficient Tumors in the Transplant Population

Neechi Okonkwo, William Tweddell. University of Maryland, Baltimore, MD.

Background: The development of colorectal cancer (CRC) proceeds via at least three molecular pathways including chromosomal instability, microsatellite instability (MSI), and CpG island methylator phenotype. MSI-associated CRC has distinct histologic features as well as a slightly better prognosis when compared to tumors without MSI. MSI is a hypermutable phenotype which is implicated in different types of cancers and is caused by deficiencies in the expression of mismatch repair (MMR) proteins. In the transplant population, the frequency of MMR-deficient CRC has not been described. By understanding the mechanisms which CRC develops, potential therapies can be optimized for this patient population that carries an increased risk.

Design: Electronic medical records were searched to identify patients with a history of both organ transplantation and development of CRC after transplantation. MMR protein expression in these individuals was evaluated using immunohistochemical staining for MMR proteins – MLH1, MSH2, MSH6, and PMS2. A lack of these proteins leaves the DNA vulnerable to mutations that can subsequently lead to cancer.

Results: Among 14 cases of CRC, 7 had a history of development of colorectal cancer after organ transplantation. 5 of 7 cases had complete or partial loss of MMR protein expression compared with no loss of expression in the controls (71.4% vs 0%, p = 0.005, Fisher’s exact test). Of the cases with loss of MMR protein expression, 100% (5 of 5 cases) had loss of MLH1 and MSH2 expression and one additionally had a loss of MSH2 and MSH6 expression.

Conclusions: This study demonstrates that HER family is a new molecular target in colorectal cancer therapy. However, this study does not provide important prognostic information, and % of HG component should be additionally detected in future studies.
767 Histological Characteristics Correlated with MSI Status in Colorectal Carcinomas: The Results of a 5-Year Prospective Evaluation

Dane Olevian, Reetesh Pai.

University of Pittsburgh Medical Center, Pittsburgh, PA.

Background: Identification of mismatch repair (MMR) protein deficiency (MMRD) in colorectal carcinomas (CRC) is advocated to screen for Lynch syndrome and is an important step in the reporting of histologic features of MMRD in CRC. The College of American Pathologists (CAP) protocol for CRC advocates the reporting of histologic features of MMRD. However, the reliability of histologic features in predicting MMRD has not been fully evaluated.

Design: 942 consecutive CRCs over a 5-year period were assessed for histologic features of MMRD (tumor infiltrating lymphocytes, Crohn-like inflammation, mucinous/signet ring differentiation, and medullary differentiation). Histologic features of MMRD were reported as present (the presence of any histologic feature) or absent (the absence of all histologic features). The results were compared with the IHC results, using standard IHC for MMRD proteins, to assess the reliability of histologic features in predicting MMRD.

Results: Table 1 details the correlation of histologic features and IHC. Histologic features of MMRD had the following test characteristics for predicting MMRD by IHC: sensitivity 73% (66-80%), specificity 78% (75-81%), positive predictive value 38% (32-44%), and negative predictive value 94% (92-96%). Importantly, the sensitivity of histologic features of MMRD in predicting MMRD by IHC was much lower in the left colon/rectum (56%) compared to the right colon (78%) (Table 2).

Table 1: Histologic Features of MMRD and MMR Immunohistochemistry

| Histologic Feature of MMRD | MMR Proficient by IHC (%) | MMR Deficient by IHC (%) |
|---------------------------|--------------------------|--------------------------|
| No of Cases               | 785                      | 177                      |
| Present                   | 174 (22)                 | 167 (27)                 |
| Absent                    | 621 (79)                 | 110 (63)                 |

Table 2: Sensitivity and Specificity of Histologic Features of MMRD in Predicting MMRD Immunohistochemistry

| Tumor Site in the Colon/Rectum | Sensitivity (%) (95% CI) | Specificity (%) (95% CI) |
|--------------------------------|--------------------------|--------------------------|
| All Sites                      | 73 (66-80)               | 78 (75-81)               |
| Right Colon / Rectum          | 78 (69-85)               | 69 (63-74)               |
| Left Colon / Rectum           | 56 (38-74)               | 83 (80-86)               |

Conclusions: Our prospective evaluation demonstrates that histologic features of MMRD do not reliably predict MMRD by IHC. This is particularly evident in tumors of the left colon/rectum. The CAP protocol should be modified to advocate for universal screening of all CRCs for MMRD given the lack of sensitivity and specificity of histologic features in predicting MMRD by IHC.
with metastatic and synchronous occurrence of GED after treatment), multiple adenocarcinomas (ADC) (n=37, group with metastatic and synchronous occurrence of adenocarcinoma after treatment). Results: Multiple GED, ADC groups revealed increased age (p=0.036) and larger size (p<0.0001) to the solitary group. Furthermore, marked intestinal metaplasia, atrophy and crypt dysplasia were more easily found in multiple GED, ADC groups compared to solitary groups (p<0.0001). Interestingly, presence of incomplete type of IM (p=0.003) and crypt dysplasia (p<0.0001) was associated with multiple GED, ADC groups.

Conclusions: Our results suggested that clinicopathological features of background mucosa, such as intestinal metaplasia, atrophy, and crypt dysplasia, could be used as indicator of occurrence of metastatic and synchronous gastric neoplasm after endoscopic treatment of gastric epithelial dysplasia. 

772 Histologic Features in Colorectal Sessile-Shaped Malignant Polyps with Nodal Metastasis

Natalie Patel, Romulo Celli, Baqu Hu, Dhanpat Jain, Yale University, New Haven, CT.

Background: Malignant polyps are defined as adenocarcinoma limited to the submucosa (pT1). It is known that tumor differentiation, lymphovascular invasion (LVI), margin status, polyp size and shape are important risk factors indicating possible lymph node metastasis, which justifies a colectomy. However, in daily practice the size, margin and LVI are often unknown or difficult to assess in a piecemeal polypectomy from sessile-shaped adenomatous polyps (SP). We aimed to evaluate morphological features in SPs, such as cribriform (CR) and micropapillary (MP) architecture and tumor budding (TB), to determine if these features portend an increase metastatic potential warranting a resection procedure.

Design: A retrospective study was carried out from a previously constructed database of patients operated on for malignant colorectal cancer between January 2008 and May 2010. The pathology database was searched to identify T1, N1 or greater colorectal carcinomas (CRC) arising from SPs from 2005-2010. Malignant SPs and their corresponding resection specimens were reviewed and the age, gender, TB, grade, morphology, tumor size and TNM stage were recorded. Malignant SPs with N0 designation were used as the control group. Sensitivity (Sn) and specificity (Sp) were calculated for each morphology and their combinations. A logistic regression model was used to calculate odds ratio for each morphology.

Results: A total of 99 cases were identified, of which 51 cases had SPs with known metastatic status. Sensitivity (Sn) and specificity (Sp) in differentiating nodal positive (N+) cases from nodal negative (N-) cases are as follow: CR: 77%, Sp: 82%; MP: 71%, Sp: 61%; HTB: 97%, Sp: 78%; CR+HTB: 83%, Sp: 84%; MP+HTB: 77%, Sp: 94%; ALL: 93%, Sp: 97%.

Conclusions: The current study showed that CR and HTB were useful in predicting nodal metastasis. Of the cases analyzed, CR and HTB were found in 38% of the nodal positive cases and in 5% of the nodal negative cases. Therefore, CR and HTB are markers of malignant potential and could be used to identify those cases in which follow up and resection were indicated.
777 Immuno-histochemical and Molecular Characterization of Dysplasia Subtypes in Ulcerative Colitis
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Background: The morphologic spectrum of dysplasia in IBD has recently expanded to include variants that are poorly characterized. Little is known about the biological features of these subtypes. The aim of our study was to assess a variety of immunohistochemical and molecular markers in different dysplasia subtypes of UC, to determine their biologic significance, and investigate potential pathways of carcinogenesis.
Design: 30 dysplastic foci [15 low-grade (LGD), 15 high-grade (HGD)] from 23 UC patients (8 M, 15 F) were reviewed and classified as: adenoma-like [elongated, pseudodisplaced nuclei (n=15)], terminally differentiated (n=4), serrated (n=7), and hypermucinous (n=4). All cases were stained for MUC2, MUC5AC, MUC6 and markers of colorectal carcinogenesis [p53, β-catenin (nuclear), annexin A10 (ANXA10), Maspin, BRAF (cytoplasmic), SOX9 (nuclear)]. Staining in ≥10% cells was considered positive.
Results: The distribution of markers in 30 dysplastic foci was: MUC2-90%, MUC5AC-0%, MUC6-7%, p53-48%, β-catenin-30%, ANXA10-17%, BRAF-7%, Maspin-87%, and SOX9-100%. Compared to LGD, HGD showed frequent MUC6 (13% vs 0%), β-catenin (40% vs 20%), ANXA10 (27% vs 6%), and p53 expression (87% vs 7%); only p53 was significant (p=0.01). After analyzing each subtype, all adenoma-like dysplasia were MUC2 positive; one case was diffusely MUC6 positive. All 4 hypermucinous dysplasias expressed MUC2, 2/4 expressed MUC6, and none expressed MUC5AC. The most commonly altered marker in adenoma-like dysplasia was p53 (33%), whereas terminally differentiated subtype showed equal p53 and β-catenin expression (50%). Majority of hypermucinous dysplasia cases (75%) showed aberrant p53. BRAF positivity was only seen in serrated dysplasia. Serrated dysplasia was most commonly associated with p53 (57%) and β-catenin (43%) expression, while ANXA10 was only seen in 14% cases. While none of comparisons were statistically significant, ANXA10 was significantly more common in terminally differentiated compared to adenoma-like dysplasia (50% vs 7%, p=0.03). None of the markers showed any significant correlation with location or endoscopic appearance of dysplasia.
Conclusions: p53 appears to play a major role in adenoma-like, terminally differentiated, and mucinous precursors in IBD related neoplasia, whereas combined alterations of p53 and β-catenin are associated with serrated precursor. As aberrant p53 is most commonly seen in HGD, it likely represents a late event in IBD carcinogenesis. While MUC2 is expressed by most dysplasia subtypes, MUC6 is a marker of hypermucinous phenotype.

778 Assessability of Endoscopic Biopsies of the Proximal Large Intestine for the Changes Diagnostic of Sessile Serrated Polyp/Adenoma
Garrison Pease, Curtis R Hall. University of Chicago - NorthShore, Evanston, IL.
Background: Given that the diagnostic criteria for sessile serrated polyp/adenoma (SSP/A) imply an ability to observe crypt bases in endoscopic biopsies (EB) of the large intestinal mucosa (LIM) (in search of the characteristic features of SSP/A), we sought to develop an understanding of the assessability for SSP/A of such biopsies in our surgical pathology files.
Design: Through search of our files and review of slides generated from biopsies of the proximal LIM, we identified cases, from a single month, in the serrated polyp spectrum (hyperplastic polyp (HP) through SSP/A) for inclusion in this study. One or both of us queried each eligible case for number of lesional crypt bases present and number of crypts with features diagnostic for SSP/A.
Results: Our results are presented in the bar graphs below:

In summary, of 182 serrated lesions identified, 30 (16.5%) had no crypt bases available for review, while 52 (28.6%) had 5 or less. Of 102 cases judged diagnostic of SSP/A, 13 (12.7%) had only 1 to 3 crypt bases with changes diagnostic for SSP/A.
Conclusions: These results indicate that the diagnosis of SSP/A is subject to sampling error in regards to the inclusion of crypt bases, wherein are most of the features characteristic of SSP/A. Sampling error, along with interobserver interpretative variation (a source of error not addressed in this study), is likely to present, in day-to-day signout, a persistent barrier to completely accurate assessment for the presence or absence of SSP/A in any one patient through histopathological review of LIM biopsies. We conclude, as others have through other methodologies, that the identification of patients...
at risk for development of LIM adenocarcinoma through the serrated polyp pathway should depend as much on endoscopic assessment of the number and size of serrated polyps as much as on the histopathological assessment of these lesions.

779 ERBB2 Alterations as a New Prognostic Biomarker in Stage III Colon Cancer (CC) from a FOLFOX Based Adjuvant Trial (PETACC8)
Frederique Penault-Llorca, Pierre Laurent-Puig, Anne-Cayre, Karine Le Malicot, Jean-Francois Billaut, Centretomie, Saint-Cloud; Hôpital Européen Georges Pompidou, Paris, France; Fédération Francophone de Cancérologie Digestive (FFCD), Dijon, France; Hôpital Ambroise Paré, Boulogne, France; Hôpital Européen George Pompidou, Paris, France.

Background: ERBB2 amplifications have been recently shown as a potential targetable alteration in metastatic colorectal cancer, in the HERACLES trial. This discovery reinforces the interest to study the occurrence and the prognostic role of ERBB2 alterations in stage III colon cancer (CC) where we need to improve adjuvant strategies. Prospective collection of PETACC8 study [EudraCT number 2005-00346-C2] allowed us to evaluate the occurrence and the prognostic impact of ERBB2 alteration.

Design: From the 2559 pts of PETACC8 trial, 2043 signed the translational research informed consent. Among them, tissues samples were available in 1795 pts for NGS screening, and 1808 were available for immunohistochemistry and FISH analysis. We searched for ERBB2 mutation in exon 19 to 21 and for amplification, using the colon cancer panelv2 and an algorithm previously validated. All cases were screened by immunohistochemistry (IHC) with PATHWAY anti-HER-2/new (4B5) from Ventana and FISH analysis (Dako HER-2 FISH SPEC-BR).

Results: Altogether, ERBB2 alterations were present in 64 pts (3.8%) and in 42 (2.6%) in the KRAS wild type group. We identified 17 mutations (1%), most frequent pV842I (3 pts), p.V777L (3 pts), p.L755S (3 pts). No significant association with RA5 or RAIP mutations nor mutual exclusivity. We identified NGS ERBB2 amplification in 49 pts (2.9%), 46 by FISH (including the 39 IHC+). Discordances were observed in the 0/1 category, 4 cases being amplified by FISH and NGS. Prognostic impact of ERBB2 alterations by pooling pts mutations or amplified: in univariate analysis, ERBB2 alterations were associated with shorter time to recurrence (HR: 1.55 [95% CI: 1.02; 2.36] p = 0.04) and shorter overall survival (HR: 1.57 [0.99; 2.5 ] p = 0.05). This prognostic value was maintained after adjustment for treatment, RA5 mutation, histological grade, tumor location, pT and pN status, bowel obstruction or perforation and embolization. Conclusion: ERBB2 alteration is a rare event found in approximately 4% of stage III CC pts. Its poor prognostic value supports the evaluation of anti-erbB2 therapies in the adjuvant setting. Due to their low frequency, screening for these alterations at NGS should show to be more cost effective than IHC and FISH.

780 Epstein-Barr Virus Infection in Inflammatory Bowel Disease Patients Undergoing Colectomy
Maryam Peychou, Ogechukwu Pearl Eze, Yuman Tarashikh, Kevin Waters, Alyssa Purian, Mark Lazarew, Elizabeth A Montgomery, Lynsandra Voltaggio. Johns Hopkins Hospital, Baltimore, MD.

Background: Inflammatory bowel disease (IBD) is a chronic inflammatory process of unknown etiology. A potential role for viral infection and associated mucosal immune response has been suggested by some studies. Infection with Epstein-Barr Virus (EBV) can elicit a broad spectrum of responses in the gastrointestinal tract. The role of this infection in patients with IBF refractory to treatment has not been fully evaluated. Design: Surgically resected colonic specimens from 52 patients with refractory IBD (48 with ulcerative colitis, 3 patients with Crohn’s disease and 1 patient with indeterminate colitis) were retrieved from our archive. Eleven colectomy specimens from ulcerative colitis patients who had undergone resections due to the presence of dysplasia or non-neoplastic small intestinal mucosa were included as controls. Highly sensitive EBV-encoded small RNA1 (EBER-1) in situ hybridization was performed on a representative block from each specimen. EBER-1 reactivity was graded as absent, focal, or diffuse.

Results: EBV was detected in 63.5% (33 out of 52) of patients with refractory IBD, compared to 18% (2 out of 11) of the control group (P-value <0.001). Focal EBER-1 positivity was present in 50% of cases of refractory IBD (26 out of 52) compared to 18.2% of control (2 out of 11). Diffuse EBER-1 reactivity was seen in samples from 7 of 52 patients (13.5%) in the refractory IBD group. None of the samples from the control group patients had diffuse EBER-1 positivity. Patients with EBER-1 positivity were older (average age of 42 years old) compared to patients without EBER-1 reactivity (average age, 32 years old) (P-value =0.039). There was no gender difference. Conclusion: EBV infections may have a potential role in patients who are refractory to IBD treatment. More studies are needed to confirm our observations.
196A ANNUAL MEETING ABSTRACTS

786 Expression of PD-1 and PD-L1 in High Grade Neuroendocrine Carcinomas Treated and Associated Host Immune Cells: A Potential Target for Anti-PD-1/PD-L1 Therapy

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Background: High grade neuroendocrine carcinomas (HGNECs) in IBD-related dysplasia are aggressive tumors that often have limited treatment options. Programmed death (PD-1) pathway plays critical role in the host immune response to cancer. Programmed death 1 ligand (PD-L1) and receptor (PD-1), expressed on tumor or immune cells, serve as a brake for potential clinical response to immune checkpoint blockade using anti-PD-1/PD-L1 therapies. Therefore, it may be advantageous to investigate the complex tumor-host immune milieu, through the expression of PD-1 and PD-L1 in IBD and immune cells, in HGNECs.

Methods: Forty-two HGNECs at various sites of the digestive system (colon, small bowel, pancreas, stomach, esophagus, gallbladder) were identified from 42 patients in our departmental archives between 1/1/97 and 6/30/15. Patient medical records, pathology reports, and pathology slides were reviewed. Immunohistochemistry for PD-1 and PD-L1 was performed on all cases (3 biopsies and 39 resections). PD-1 and PD-L1 positivity was defined as ≥ 1% cell surface expression of PD-1/PD-L1 by tumor cells and/or peri-tumor-immune cells (lymphocytes and histiocytes).

Results: Mean age of the patients was 61.8 years, ranging from 32 to 80. Overall 16 of 42 (38.1%) cases had PD-L1 expression by tumor cells and/or inflammatory cells. Nine of 42 (21.4%) were positive for PD-L1 in IBD cells. Positive correlation was seen between PD-L1 expression in tumor cells and tumor-host immune cells in 45.2% (19/42) of cases. PD-L1 expression was significant in 13% (6/42) cases. PD-L1 expression was significant in 13% (6/42) cases. PD-L1 expression was significantly associated with PD-L1 expression in tumor cells and PD-L1 expression in immune cells (p=0.007). PD-L1 expression was significantly associated with PD-L1 expression in tumor cells and PD-L1 expression in immune cells (p=0.007). PD-L1 expression was significantly associated with PD-L1 expression in tumor cells and PD-L1 expression in immune cells (p=0.007).

Conclusions: The expression of PD-L1 in HGNECs may be a potential target for immune checkpoint blockade using anti-PD-L1 therapy. Further studies are needed to determine the role of PD-L1 in the immunogenicity of HGNECs.

787 Adenocarcinoma Ex-Goblet Cell Carcinoid of the Appendix Is a Tumor of Intestinal Lineage and Mucinous Differentiation

Brian Robinson, Bahar Memis, Andy Toussaint, Yue Xue, Alyssa Krasinskas, Charles Staley, Joshua H Winer, Maria C Bassell, Waldal Shabt, Bassel El-Bayat, Voltan Adsay, Michelle D Reid. Emory, Atlanta, GA.

Background: Appendiceal adenocarcinoma ex-GCC (XGC) is a highly aggressive tumor of debated nature and origin, that has been shown to have very high propensity for peritoneal dissemination and intraperitoneal carcinomatosis (and “Krukenberg” type spread to gynecologic tract (PMID: 27378863), and thus commonly falls in the differential diagnosis with gastric and other signet ring carcinomas. The data regarding the immunophenotypic differentiation and cell lineage of XGC is highly limited with conflicting results.

Design: Upon IHC approval, immunohistochemistry (IHC) was performed on all tumors. The data were further analyzed using Perl (vs WDDNETs), namely RB loss and p53 over-expression, were detected in 52% and 46%, respectively. Moreover, IHC antibodies auxilliary markers were used in both groups.

Results: Results: Results: Results: Results:

Conclusions: The aggressive nature of HGNECs and limited treatment options suggest that targeting PD-L1 may be an option in select patients with HGNECs.

788 Invasive Adenocarcinoma Arising from Low-Grade Appendiceal Mucinous Neoplasms: Clinicopathologic Features

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Background: Primary appendiceal mucinous lesions are uncommon and represent a spectrum from non-neoplastic mucous retention cysts to invasive adenocarcinoma. The precise nomenclature and management of various appendiceal mucinous lesions is controversial. Here, we describe cases of invasive appendiceal adenocarcinoma arising in a background of low grade appendiceal mucinous neoplasm (LAMN).

Design: The pathology database was searched to identify cases of adenocarcinoma arising in the appendix with background LAMN in the last 2 years based on criteria summarized in the 2016 Peritoneal Surface Oncology Group International Consensus.

Clinicopathologic features were then assessed.
ANNUAL MEETING ABSTRACTS

789 Immune Checkpoint Expression and the Tumor Immune Environment in Colorectal Carcinoma
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Programmed Cell Death Protein 1 axis blockade enhances anti-tumor immunity, leading to clinical response in microsatellite instability (MSI)-high colorectal cancer (CRC). Tumor cell expression of Programmed Cell Death Ligand 1 (PD-L1) interacts with the expression of PD-1 on the surface of T cells. In this study, PD-L1 expression was associated with treatment response in various tumor types. The association and biological role of additional, potentially actionable immune inhibitory targets, such as Indoleamine 2,3-Dioxygenase 1 (IDO1) and PD-1H4, is not well understood in CRC.

Design: A tissue microarray consisting of multiple cores from 171 cases of CRC was analyzed for PD-L1, IDO, and B7H4 expression on tumor cells by immunohistochemistry using H-scores (graded as percentage of cells expressing 0, 1+, 2+, or 3+ staining of a total of 0-300). CD8, TETB (a Th1 pathway activation marker), and CD4 (a Th2 pathway activation marker) positive tumor infiltrating lymphocytes (TILs) were dichotomized (abundant or not). For each case, clinicopathologic data and follow-up was reviewed.

Results: Using a cut-off H score of ≥5, 18 (11%) cases expressed both PD-L1 and IDO1, 44 (16%) expressed only PD-L1, 128 (75%) did not express either. No cases showed positive B7H4 expression. Compared to PD-L1/IDO negative tumors, PD-L1-only expressing tumors were associated with abundant TETB+ TILs (p=0.02), TP53 mutation (p<0.03), and medullary phenotype (p<0.03). Compared to PD-L1/IDO negative tumors, IDO-only expressing tumors occurred in older patients (p<0.03), primary resections lacking pre-collection therapy (p<0.02 each), and had abundant CD8+ and TETB+ TILs (p=0.005 for both), with a medullary phenotype (p=0.01) and MSI (p<0.001). Clinicopathologic features of IDO1 and/or PD-L1 pathway activation marker positive tumor infiltrating lymphocytes (TILs) were dichotomized (abundant or not). For each case, clinicopathologic data and follow-up was reviewed.

Conclusions: IDO1 expression with or without PD-L1 expression is common in CRC, and is associated with the immune microenvironment and MSI that have been reported in immune response to PD-L1 expression. Thus, IDO1 may be a mechanism of immune resistance providing normally immunogenic colorectal carcinoma a means of immune evasion. Thus, blockade of IDO1 may represent a potent therapeutic strategy to reactivate anti-tumor immunity in CRC. In addition, the difference in TP53 mutation rate between IDO+ and PD-L1+ populations implies that a different pathogenic mechanism may underlie the expression of these molecules.

790 HER2 Driven Colorectal Cancer: A Comprehensive Genomic Profiling Study
Christoph Rosty, Mark Clendenning, Steven Gallinger, Mark Jenkins, Kevin Sweet, Finlay Macrae, Ingrid Winship, Susan Parry, Daniel Buchanan. Enviio Pathology, Brisbane, Australia; University of Melbourne, Melbourne, Australia; University of Toronto, Toronto, Canada; Ohio State University Medical Centre, Colombus, OH; New Zealand Familial Gastrointestinal Cancer Service, Auckland, New Zealand.

Background: Mismatch repair (MMR) protein deficiency is the hallmark of colorectal carcinoma (CRC) in Lynch syndrome patients and sporadic CRC with MLH1 methylation. Patients with an MMR-deficient CRC who have no deleterious germline variant are grouped under the category of Lynch-like syndrome. Biallelic somatic alterations in a DNA MMR gene are one possible cause for MMR deficiency in Lynch-like syndrome.

Design: CRC cases from two large population-based cohorts have been tested for MMR protein deficiency and MLH1 methylation for MMR-deficient tumors. Tumors from Lynch-like syndrome patients were selected for somatic mutation screening in DNA MMR genes using Custom AmpliSeq panel and sequencing, and for loss of heterozygosity (LOH) using Affymetrix Oncoscan array.

Results: From an initial cohort of 1639 CRC patients tested for MMR protein deficiency, 63 Lynch-like syndrome patients were identified and 50 tumors were successfully tested. Biallelic somatic alterations were identified in 18 cases (36%), a single somatic alteration in 24 cases (48%), and no somatic alterations in 7 cases (14%). The percentage of CRC with biallelic somatic alterations was higher for MSH2-deficient tumors (15/10, 50%) and MLH1-deficient tumors (12/31, 39%), compared with MSH6-deficient tumors (1/6, 0%) and PMS2-deficient tumors (0/3).

Conclusions: Biallelic somatic alterations in DNA MMR genes account for a significant proportion of Lynch-like syndrome patients and, when present, exclude Lynch syndrome. However, the majority of Lynch-like syndrome cases remain unexplained. In particular, a single somatic alteration can be associated with a missed second hit that can be either somatic or germline, therefore not excluding Lynch syndrome.
794 Interobserver Variability of Histopathological Regression Scoring Systems Following Neoadjuvant Chemo-Radiotherapy in Esophageal Cancer

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Background: Neoadjuvant chemoradiotherapy (NACRT) is the treatment of choice in operable esophageal carcinoma (EC), with significant improvement in survival compared to surgery alone. Though tumour regression grade (TRG) is well-documented as a prognostic indicator, consistent reporting remains a challenge. The aim of this study was to assess the response to treatment, and interobserver concordance using 6 common TRG systems (Table 1).

Design: We reviewed the histological parameters of consecutive cases of EC who received NACRT followed by esophagectomy at our center. All patients were treated with radiotherapy and concurrent paclitaxel-carboplatin based chemotherapy. We reviewed the histological parameters of consecutive cases of EC who received NACRT followed by esophagectomy at our center. All patients were treated with radiotherapy and concurrent paclitaxel-carboplatin based chemotherapy.

Results: 38 patients (35 Squamous carcinomas, 2 Adenocarcinoma, NOS, 1 Adenocarcinoma) showed median age of 56.5 years and predominantly mid-esophageal involvement. 34.2% patients showed complete pathological response as per Modified Ryan classification. The vast majority of CRCs with MLH1/PM2 loss were diagnosed in patients older than 70 years (83.8%), most of them are likely to be sporadic MLH1 methylation. In 8 cases with MLH1/PM2 loss, loss of MSH6 expression was also present. The percentage of CD4 and CD8 cells were not increased in small intestinal allografts. The percentage of CD163 positive cells was increased in all age groups, including many in those excluded by current guidelines. Further studies are needed to demonstrate the actual rate of Lynch syndrome individuals identified from this initial screening.

795 Macrophage Aggregation Is a Sallent Feature of Acute Rejection in Small Intestinal Allografts

Natalia Bush, Chandrakshar Katabal, Romil Saxena. Indiana University School of Medicine, Indianapolis, IN.

Background: Small intestinal transplantation is an accepted therapeutic modality for end-stage intestinal failure. The aim of this study was to characterize the inflammatory infiltrate in the lamina propria of small intestinal allografts undergoing rejection.

Design: We retrieved biopsies with a diagnosis of acute rejection from the pathology database. Biopsies of native and allografted small intestine with no pathological change served as controls. Immunohistochemical stains for CD4, CD8 and CD163 were performed. Each marker was evaluated as a percentage of the total number of inflammatory cells in the lamina propria.

Results: The percentages of CD4 and CD8 cells were not increased in small intestinal allograft biopsies. Percentage of CD8 positive cells was decreased in some allografts, attributable to immunosuppressive medications. The percentage of CD163 positive cells was increased in the allografts. These macrophages were present as aggregates in 82% (14/17) of the allograft biopsies. Macrophage aggregates were also seen in one of five control biopsies. This biopsy was from a small intestinal allograft and showed no pathologic change on hematoxylin-eosin.

796 Multinucleated Giant Cells in the Gastroesophageal Junction and Gastric Mucosa

Tala Sachak, Wendy L Frankel, Christina Arnold, Wei Chen. The Ohio State University Wexner Medical Center, Columbus, OH.

Background: In our clinical practice, we occasionally encounter multinucleated giant cells (MGCs) in the gastroesophageal junction (GEJ) and gastric mucosa. MGCs contain hyperchromatic, overlapping nuclei, and variable cytoplasm. Little is known about the origin and significance of these cells. Our goal is to identify the origin of MGCs using immunohistochemistry, determine their clinicopathological associations, and therefore improve diagnostic accuracy and avoid pitfalls.

Design: 352 contiguous biopsies and 1 resection specimen from stomach and GEJ were identified from archives in January 2016. Patient age, sex, clinical indication for endoscopy, and pathologic diagnosis were noted. The number of MGCs per 10 high power fields (HPF) was recorded. 17 MGC cases (6 stomach; 11 GEJ) were immunostained for smooth muscle actin (SMA), desmin, CD117, S100, cytokeratin AE1/3, chromogranin, and CD68.

Results: MGCs were identified in 22 cases (7 gastric, 15 GEJ; 5.6%). Patients’ average age was 53 years. Male/female ratio is 1.2:1. Most cases (64%) have only 1 or 2 MGCs per 10 HPF. MGCs are located in the lamina propria of the gastric/GEJ mucosa, with an accentuation in the subepithelial zone. The median number of nuclei in a MGC is 5 (ranging from 3 to 16). The nuclei are touching/overlapping, often arranged around “wreath” or “caterpillar” configurations. Cytoplasm is variable from scant to moderate. MGCs appear to be in continuation with the upward stranding muscularis mucosae in some areas. MGCs are positive for SMA, desmin, while negative for cytokeratin AE1/3, CD68, S100, chromogranin, and CD117. Most common clinical history is epigastric pain, gastrointestinal reflux, and Barrett esophagus. Most common associated pathologic diagnosis is reactive (chemical) gastrophy (71% gastric biopsies) and gastrointestinal reflux (73% GEJ specimens).
797 Difference of Histological Alteration Between Preoperative Chemoradiotherapy and Chemotherapy, and It's Clinical Implication

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National Center Hospital East, Kashiwa, Chiba, Japan.

Background: The aim of the study was to elucidate difference in the histological features and clinical outcome between preoperative chemoradiotherapy and chemotherapy in patients with rectal cancer.

Design: One-hundred-twenty-eight patients who underwent surgery for rectal cancer were included in the study. Thirty-eight patients received preoperative chemoradiotherapy (CRT group), 44 patients received preoperative chemotherapy (CT group), and 46 patients received surgery alone (SA group). Differences of histological features, clinicopathological features and clinical outcomes were compared among three groups.

Results: Total number of 53 neoplasms were included in the study. Age of patients based on histopathology reports. The cases included in the study were primary appendiceal tumors which had preoperative CT scan reports. Metastatic tumors of the stomach (n=16), colon (n=20), and appendix (n=13) were also included.

Conclusions: Different histological features after CRT and CT groups are much different. This study provides useful prognostic information regardless of the variation of preoperative therapy.

800 Radio-Pathologic Correlation on CT Scan Findings for Appendiceal Tumors: Width of the Appendix the Most Important Clinching Factor

Deepika Savant, Cristina Sison, Sharon X Liang, Cathy Fan. Hofstra-Northwell School of Medicine, Lake Success, NY.

Background: Radio logical findings play an important role in guiding the hand of a pathologist. We aimed to highlight the accuracy and hence the dependability on CT scan reports for appendiceal tumors.

Design: A retrospective study of the appendiceal lesion was done for the past 3 years based on histopathology reports. The cases included in the study were primary appendiceal tumors which had preoperative CT scan reports. Metastatic tumors of the stomach, colon, and appendix were also included.

Results: Total number of 53 neoplasms were included in the study. Age of patients ranged from 18-89 years (mean 57.7) among 37 females and 16 males. Majority of the tumors were less than 10 cm, diffusely involving the appendix; underwent appendectomy (n=40), right hemicolecction (n=7), cecectomy (n=6). Incidental lesions were seen in 18.8%. On correlating with the CT scan reports, 43.39% (n=23) did not contain the radiology findings in IM patients. We used Mann-Whitney test was used to compare continuous variables between groups. Sensitivity, Specificity and predictive values and their corresponding 95% confidence intervals were calculated.

Conclusions: Total number of 53 neoplasms were included in the study. Age of patients ranged from 18-89 years (mean 57.7) among 37 females and 16 males. Majority of the tumors were less than 10 cm, diffusely involving the appendix; underwent appendectomy (n=40), right hemicolecction (n=7), cecectomy (n=6). Incidental lesions were seen in 18.8%. On correlating with the CT scan reports, 43.39% (n=23) did not contain the radiology findings in IM patients. We used Mann-Whitney test was used to compare continuous variables between groups. Sensitivity, Specificity and predictive values and their corresponding 95% confidence intervals were calculated.
thickness, volume, tumor size, site, TNM stage, type of surgery performed and clinical findings. The sensitivity and specificity of accuracy of each type of tumor was assessed, but were found to have low precision due to limited sample size.

Conclusions: Gross width is the most important factor in clinching the diagnosis in radiological findings. However, for other appendiceal lesions which do not distort the appendix, histopathology is still the most important tool for diagnosis. This study will be used during a larger cohort for validation of the results.

801 Antibody Mediated Rejection in Intestinal Transplant: A Correlation of Histology with Donor Specific Antibodies

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Background: Intestinal transplantation (ITx) is a life-saving treatment option for selected patients with intestinal failure. However, graft failure remains high compared to other solid organ transplants with allograft rejection presumably by T-cell mediated processes. Antibody mediated rejection (ACMR) is the leading cause. While antibody mediated rejection (AMR) in the presence of donor specific antibodies (DSA) is a recognized complication, the significance of DSA and AMR in ITx is largely unknown. This study aims to investigate DSA in ITx and find histologic correlates that may help in elucidating the role of AMR in ITx.

Design: We retrospectively examined 21 biopsies and 1 resection ITx specimen from 2015-16 and categorized them according to DSA status and graft dysfunction (GD). ITx occurred from 2003-2016. Cases were randomly selected from four different categories: 1) DSA present with no GD (DSA+GD-), 2) DSA present with GD (DSA+GD+), 3) DSA absent with GD (DSA-GD+), and 4) DSA absent without GD (DSA-GD-).

Conclusions: The presence of DSA has been shown to correlate with clinical graft appearances in the GIT when compared to the lung. The significance of DSA and AMR in ITx is largely unknown. This study aims to investigate DSA in ITx and find histologic correlates that may help in elucidating the role of AMR in ITx.

802 Gene Profiling of Precursor Serrated Polyps and Associated Carcinoma Using Next Generation Sequencing

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Background: The serrated neoplasia pathway accounts for 30% of colorectal cancers and is initiated by BRAF activating mutations with 3 serrated precursor polyps involved: hyperplastic polyp, sessile serrated adenoma (SSA) and traditional serrated adenoma (TSA). The aim of this study was to investigate serrated precursor polyps and associated adenocarcinomas by Next Generation Sequencing (NGS).

Design: Seven precursor polyps (2 SSA and 5 TSA) and 2 TSA with an associated carcinoma were examined. Tissue was macrodissected from the precursor polyps and invasive carcinoma components using unstained, formalin-fixed, paraffin-embedded sections. DNA (≥250ng) was extracted using Qiagen’s QIAamp DNA Micro Kit. DNA samples were run on panel complete exonic sequence for 555 genes as well as intronic and exonic sequence for select genes known to be commonly involved in translocations. Sequencing was performed using the Illumina NextSeq 550 sequencer. NGS data was processed using the UHN-Clinical Laboratory Genetics custom bioinformatics pipeline, and filtered through the Cartagenia Bench Lab NGS (v4.2) software.

Results: See table 1.

| Case # | Age | Sex | Precursor lesion | Carcinoma | 6 of variants | Carcinoma |
|-------|-----|-----|-----------------|-----------|---------------|-----------|
| 1     | 83  | F   | SSA + LEDG      | 30        | no            | no        |
| 2     | 40  | M   | TSA             | 8          | no            | no        |
| 3     | 64  | F   | TSA             | 34         | no            | no        |
| 4     | 75  | M   | TSA + carcinoma | 94         | yes           | yes       |
| 5     | 59  | M   | TSA + carcinoma | 11         | yes           | yes       |

Variants in genes occurring in both TSAsts and the associated cancers showed: BRAF V600E in the precursor lesion, and variants in BRAF, PIK3CA, PRDM1, TAF1L1, CDH123, RNF43, SMAD4, STK11, CHEK2, KDM6A in the invasive adenocarcinoma. BRAF V600E was the only mutation seen in all samples across all cases. The APC T1556M*3 mutation was present in 3 out of 5 TSAsts, one of which was associated with invasive carcinoma. Three cases had RNF43 variants seen in 2 TSAsts (2 different RNF43 mutations).

Conclusions: This preliminary study using NGS is the first to demonstrate a marked increase in the number of genes altered between the type of precursor polyp, dysplasia and adenocarcinoma. BRAF V600E is the only variant seen consistently in precursor lesions and associated dysplasia or invasive adenocarcinoma at high allele frequencies. The same APC gene variant, T1556M*3*, is seen in 3 TSAsts. Genetic alteration in RNF43, a component of the Wnt pathway is seen in 2 of 5 TSAsts. APC and RNF43 gene variants may result in perturbation of the Wnt pathway and play an important role in the pathogenesis of these lesions.

803 Crospovidone and Microcrystalline Cellulose: A Novel Description of Pharmaceutical Fillers in the Gastrointestinal Tract

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Background: Pharmaceutical fillers are inactive substances incorporated into medications to facilitate drug delivery. We report the first study of the fillers crospovidone and microcrystalline cellulose (MCC) in the gastrointestinal tract (GIT).

Design: We examined 503 in-house GIT cases from 261 patients between 09/11/2015-10/23/2015, and identified 29 cases of crospovidone and or MCC from 26 patients based on previously described morphology at other sites. The control group consisted of an equal number of site matched specimens. One case was subject to special stains (Table 1). To confirm the histologic diagnosis, a variety of purified fillers and medication tablets were histopathologically processed.

Results: The fillers were found in 10% of patients, and there were no specific clinicopathologic associations. Among all study specimens, the fillers were most common in the colon ( overrun= 58.6%, S>20.6%, esophagus= 10.3%, stomach= 10.3%). On HE, crospovidone is nonbirefringent and has a coral shape with a pink core and purple coat; MCC is clear and brightly birefringent with a matchstick shape. Identical material was seen in the processed crospovidone and MCC powder and oxydodone-acetaminophen and omeprazole tablets.

Conclusions: In summary, crospovidone and MCC are common, biologically inert substances most often seen in the colon. Their presence outside of the bowel may serve as a marker of perforation. Awareness is also important to distinguish them from parasites, calcifications, and other medications. We report a unique histochemical profile as a helpful diagnostic aide, and caution that the fillers have slightly divergent appearances in the GIT when compared with the lung.

Table 1: Morphologic and Histochemical Profile of Crospovidone and Microcrystalline Cellulose

| Shape | Coral | Rod, Match-stick |
|-------|-------|-----------------|
| Polarized Light | Non-birefringent | Brightly-birefringent |
| Refractile | No | Yes |
| Alcian Blue | Bright pink | Light blue |
| Von Kossa | Dark brown | Light pink |
| Mucicarmine | Yellow center with red outline | Clear |
| Movat | Yellow | Yellow |
| Fontana-Mason | Black | Clear |
| PAS and PAM | Grey-blue | Light purple |
| APB | Tan-pink | Light blue |
| GMB | Brown-black | Brown-black |
| Congo Red | Dark orange, without apple green birefringence | Light salmon, without apple green birefringence |

804 Effects of Interobserver Variability and Subspecialty Signout on Diagnosing Microscopic Colitis

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Background: Microscopic colitis (MC) is a diagnostic category that includes lymphocytic colitis (LC) and collagenous colitis (CC). The colon is endoscopically normal in MC; diagnosis requires microscopy. Proposed criteria include increased lamina propria cellularity and more than 20 intraepithelial lymphocytes per 100 enterocytes for LC; and subepithelial collagen thicker than 10µ for CC. Studies have shown a small degree of interobserver and intraobserver variability in diagnosing MC, suggesting some subjectivity. This has not been evaluated in the context of subspecialty signout (SSSO) or a group consensus.

Design: We reviewed 133 colon biopsies diagnosed as LC, CC, MC, or normal but with mild changes insufficient for MC. All predated true SSSO at our institution. For each, we recorded original diagnosis and whether the subspecialty histopathologist had subspecialty training in gastrointestinal (GI) pathology. HE slides from all 133 were independently reviewed by 3 pathologists with GI subspecialty training, rendering diagnoses of LC, CC, or normal. Cases lacking independent consensus by this method were reviewed by the same 3 pathologists via consensus conference to establish a diagnosis. Consensus diagnoses were compared to the originally rendered diagnoses and to the independent diagnoses of the consensus pathologists.

Results: Consensus diagnoses for the biopsies were normal (n=34), LC (n=57), and CC (n=42). “Normal” cases were most commonly agreed upon by the 3 reviewing pathologists prior to consensus (27/34 cases, P=0.0073 vs. LC, P=0.0172 vs. CC).
ANNUAL MEETING ABSTRACTS

805 Expression of Epithelial-Mesenchymal Transition Markers E-Cadherin and Vimentin in Esophageal Adenocarcinoma and Squamous Cell Carcinoma and Significant Association with New Proliferation Markers MCM4 and MCM7

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Background: Epithelial-mesenchymal transition (EMT) plays a key role in the invasion of carcinoma. Loss of E-cadherin and acquisition of vimentin are two critical steps in EMT. Our study evaluated their expression in esophageal adenocarcinoma (EAC) and squamous cells carcinoma (ESCC) and precancerous lesions.

Design: TMA of 110 EAC, 23 ESCC, 66 squamous epithelium (SE), 68 columnar cell metaplasia (CM), 37 Barrett’s esophagus (BE), 27 low-grade dysplasia (LGD) and 11 high-grade dysplasia (HGD), were immunohistochemically stained for both E-cadherin and Vimentin. E-cadherin and Vimentin were scored for positive, negative and for percentage (0-100%) of positive cells.

Results: Of 110 EAC cases, 90% (n=99) were positive for E-cadherin and 3% (n=3) were positive for vimentin. Of the 23 ESCC, 100% (n=23) were positive for E-cadherin and 9% (n=2) positive for both E-cadherin and vimentin. In the EAC group, the mean survival time for E-cadherin positive cases was 38.8 months vs 48.3 months for E-cadherin negative cases although it was not statistically significant. The mean percentage of E-cadherin expression was significantly higher for ESCCC (70.2%) compared to EAC (52%). No significant difference was seen between E-cadherin expression in EAC and other precancerous lesions including BE, LGD and HGD. Loss of E-cadherin in EAC correlated significantly with higher proliferation (MCM4 = 63.9% and MCM7 = 74%); compared with E-cadherin positive cases also had a significantly higher proliferation (MCM4 = 72.2% and MCM7 = 42.2%). Vimentin positive EAC cases also had a significantly higher proliferation (MCM4 = 87.5 %) compared with vimentin negative cases (MCM4=42.8%). There was no significant relationship between either E-cadherin or vimentin expression with any clinicopathologic features.

Conclusions: EMT transition existed in low percentage of EACs and ESCC cases. A loss of E cadherin expression and expression of vimentin are associated with significantly increased proliferation.

806 Targeted Next-Generation Sequencing Supports Epidermoid Metaplasia of the Esophagus Is a Precursor to Esophageal Squamous Neoplasia

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Background: Esophageal epidermoid metaplasia (EEM) is a rare condition that involves the middle-to-distal esophagus. It is sharply demarcated and defined by the presence of prominent granular cell layer and superficial hyperkeratosis. In addition, studies have suggested a possible association between EEM and squamous dysplasia and squamous cell carcinoma (ESCC). However, whether EEM represents a preneoplastic lesion is unknown. In order to further characterize EEM and define its relationship to squamous neoplasia of the esophagus, we performed targeted next-generation sequencing (NGS) of specimens with EEM, adjacent HGSD and ESCC.

Design: Of 23 ESCC, 100% (n=23) were positive for E-cadherin and 9% (n=2) positive for both E-cadherin and vimentin. In the EAC group, the mean survival time for E-cadherin positive cases was 38.8 months vs 48.3 months for E-cadherin negative cases although it was not statistically significant. The mean percentage of E-cadherin expression was significantly higher for ESCCC (70.2%) compared to EAC (52%). No significant difference was seen between E-cadherin expression in EAC and other precancerous lesions including BE, LGD and HGD. Loss of E-cadherin in EAC correlated significantly with higher proliferation (MCM4 = 63.9% and MCM7 = 74%); compared with E-cadherin positive cases also had a significantly higher proliferation (MCM4 = 72.2% and MCM7 = 42.2%). Vimentin positive EAC cases also had a significantly higher proliferation (MCM4 = 87.5 %) compared with vimentin negative cases (MCM4=42.8%). There was no significant relationship between either E-cadherin or vimentin expression with any clinicopathologic features.

Conclusions: EMT transition existed in low percentage of EACs and ESCC cases. A loss of E cadherin expression and expression of vimentin are associated with significantly increased proliferation.

807 Genome-Wide Copy Number Aberrations Analysis Reveals Recurrent High Copy Number Gain of PTGER4 Gene in Colonic Mixed AdenoNeuroEndocrine Carcinoma and NeuroEndocrine Carcinoma

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Background: Mixed AdenoNeuroendocrine Carcinoma (MANEC) and Neuroendocrine carcinoma components. The prognosis of MANEC is distinctly worse than conventional colon adenocarcinoma (ADC). For a clinician, the major challenge is whether a patient with MANEC should be managed as conventional ADC or NEC. To explore the clinicobiological processes of these tumors, we analyzed genome-wide copy number aberrations (CNA) in MANEC and NEC. The results were then compared to CNA in ADC, obtained from published literature, including data from TCGA (The Cancer Genome Atlas).

Design: A total of 24 tumors (18 MANEC and 6 NEC) were identified. Genomic DNA from nineteen tumors (14 MANEC and 5 NEC) with known microsatellite instability and BRAFV600E mutation status were subjected to genome-wide CNA analysis using a molecular inversion probe single-nucleotide polymorphism assay (Affymetrix OncoScan assay). Results were analyzed using Nexus Copy Number software with a built-in statistical GISTIC (genomic identification of significant targets in cancer) algorithm. A genomic region with recurrent high copy number (CN) gain (4 copies or more) was further analyzed by an interphase FISH (fluoresce in situ hybridization) assay on all 24 tumors.

Results: Recurrent CNA in MANEC were gain on chromosome (chr) 5p (10/14 cases), 20q, 13q, 7, 8q and loss on chr 1p, 4q, 5q, 18q; in NEC gain were on chr 7q, 8q, 15q and loss on chr 4p, 5p, 7p. Application of statistical GISTIC algorithm identified four significant regions that may drive MANEC and NEC tumorigenesis: 5p21.1 (n=2), 13q12, 20q13 and 5p11.3. PIK3CA (n=3), PTGER4 (n=2) and EGFR (n=2) were the top three genes in the selected high CN gain regions. PTGER4 (prostaglandin E2 receptor 4) gene on 5p13.1 was identified in 4 MANECs and two NECs (6/19). Two of the tumors (one MANEC and one NEC) harbor PTGER4 gene amplification of up to 33 copies. In contrast, there was only 1% (6 of 611) of the intestinal colonic adenocarcinoma in TCGA database harbor PTGER4 gene amplification. The result of FISH assay, using CEP5 and a custom-designed probe confirmed recurrent high CN gain of PTGER4 gene on 5p13.1 suggests a potential role of inflammatory stimulation by PTGER4 up-regulation in tumorigenesis of colonic MANEC and NEC.

808 Deep Inflammation in Clinically Diagnosed Ulcerative Colitis (UC) Resections: How Much Is Too Much?

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Background: Making the correct diagnosis of UC on resection is important for proper postoperative management. We examined resection specimens from patients with a clinical diagnosis of UC and assessed for the presence, type, and distribution of inflammation within the muscularis propria (MP) and pericolonic soft tissue (ST) and its influence on diagnosis.

Design: 51 total colectomy resections (1/5 to 6/16) in clinically diagnosed UC patients were reviewed by 2 pathologists blinded to the original diagnosis. Pertinent clinical histories, including drug therapy, were noted. The cases were diagnosed as either UC or indeterminate colitis (IC) and the extent of deep inflammation, including ST lymphoid aggregates (LA), MP LA, perivascular inflammation (PVI), deep acute inflammation (AI) and ulceration extending from mucosal surface into MP (UMP) were noted. The number of LA (defined as a collection of lymphocytes easily visible on 2.5x) in the MP and ST were noted on one representative slide (RS) and subjected to statistical analysis (student’s t-test).

Results: See tables 1 and 2.
Conclusions: More than 50% of UC cases show deep inflammation on resection. In path confirmed UC, the number of MP LA (p=0.04) and ST LA (p=0.01) is related to the severity of the active colitis. There was no association between drug therapy, PV1 and PV2. Cases diagnosed as IC showed increased numbers of LA compared to UC cases, however deep AI and UMP were more likely to garner a diagnosis of IC. In summary, PV1 and MP/ST LA are exceedingly common in UC resections and their presence should not prevent a diagnosis of UC.

Background: Adenosquamous carcinoma of the pancreas (ASCP) is a rare variant of pancreatic ductal adenocarcinoma (PDAC) and has particularly poor prognosis. Little has been known about the genetic features of ASCP and drivers of this unique manifestation of PDAC.

Design: A total of 112 surgically resected PDA cases including 14 ASCP cases were analyzed by whole-exome sequencing. Somatic point mutations and insertion/deletion of DNA specific to tumor were identified using the MuTect and VarScan2 algorithms respectively. Copy number changes were determined using the Affymetrix Oncoscan FFPE platform and analyzed using Nexus Copy Number (BioDiscovery).

Results: MYC oncogene amplification, detected by whole-exome sequencing, was found in 14% of 112 PDA and 57% of 14 ASCP. FLG1 mutation (29%) was also significantly enriched in our ASCP cohort. In contrast genes canonically altered in PDAC (i.e. KRAS, TP53, CDKN2A, and SMAD4) were preferentially altered in ASCP (Figure 1A). The amplification of MYC oncogene was associated with poor outcome across the cohort (Figure 1B). In the validation TCGA cohort, amplification of MYC and FLG1 mutations were also frequently identified and associated with poor-outcome (Figure 2). TISSH analysis of additional ASCP cases, confirmed frequent MYC amplifications and showed that 77% (7 of 9 cases) of PanIN lesions coexisting with ASCP have copy increase or amplification of MYC.

Conclusions: These findings suggest that specific genetic features contribute to ASCP biology and poor outcome. In particular, MYC amplification occurs relatively early as a likely driver in the oncogenesis of ASCP.

810 Structural Genomic Changes in IBD-Related Dysplasia and Preceding Copy Number Alterations in Corresponding Non-Dysplastic Mucosa

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Background: IBD-related dysplasia has a higher rate of progression and of concomitant neoplasia relative to sporadic lesions. Using Molecular Inversion Probe technology, formalin-fixed paraffin-embedded (FFPE) biopsy tissue can be processed to identify structural genetic changes using the Affymetrix Oncoscan for FFPE platform, allowing comparison of changes in non-dysplastic and dysplastic colonic mucosa of IBD harvested over years of endoscopic screening. Our aim was to use this platform to explore the molecular alterations of dysplasia and those that may precede its development in IBD.

Design: Seven cases with ≥3 years of endoscopic surveillance and IBD-related dysplasia (6 low-grade (LGD) and 1 high-grade (HGD)) plus controls were selected. Each case included biopsies of dysplastic mucosa and concurrent non-dysplastic mucosa away from the site of dysplasia, as well as prior non-dysplastic mucosa (collected within 3 years of dysplasia) at the same site. The epithelium was microdissected and FFPE sample-derived DNA was isolated. The DNA was processed using the Affymetrix ONCOSCAN for FFPE platform and analyzed using Nexus Copy Number (BioDiscovery).

Results: Three cases of dysplasia showed significant alterations, including large segments of loss of heterozygosity (LOH) or copy number alterations (CNA) at 5q, 14q, and 20q in one case of LGD, CNA at 1q and 17q in another LGD and multiple complex alterations in HGD. In the corresponding non-dysplastic samples (both concurrent and prior) of the LGD cases, we identified short regions of CNA with the same point of origin as the long regions of LGD seen in dysplastic mucosa: a 0.5Mb region in 17q, which included BRCA1, and a 0.7Mb and 2.3Mb region in 5q. These may represent precursor genomic structural changes and were not found in controls.

Conclusions: This study found small regions of CNA in non-neoplastic mucosa with the same sites of origin as large regions of LGD found in dysplasia. The discovery of these small, potentially pathogenic regions is novel. Additional studies will confirm and functionally characterize these sites. FFPE biopsy samples are a useful resource in studying the progression of molecular changes that takes place in the development of IBD-related dysplasia. This can shed light on the predictive value of molecular findings in non-dysplastic mucosa and help identify IBD patients at higher risk for progression to colorectal neoplasia.

811 Type-1 Gastric Neuroendocrine Tumors: Long-Term Follow-Up and Non-Specific ER and GATA-3 Expression

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Background: Gastric well differentiated neuroendocrine (carcinoid) tumors (Type-1 gNETs) are indolent, arising in the setting of ECL-cell hyperplasia due to hypergastrinemia from autoimmune metaplastic atrophic gastritis (AMAG). A recent report found that 33 of 75 Type-1 gNETs had Ki67 proliferation indices of <2% as criteria for grade 2 (>2%), but it is not known if these tumors have worse behavior. Also, Type-1 gNETs are composed of loosely cohesive cells in the lamina propria raising the differential diagnosis of metastatic lobular breast cancer. To our knowledge, immunohistochemistry for breast cancer markers has not been evaluated in these tumors.

Design: We have identified 26 Type-1 gNETs from 17 patients from our in-house surgical pathology service between 1997 and 2005. Basic demographic data were collected and patient charts were mined for evidence of metastatic disease or mortality. IHC was used to stain for Ki67, ER, and GATA-3.

Results: There were 26 Type-1 gNETs from 17 patients with long-term follow-up for evidence of disease progression and immunohistochemical (IHC) staining for breast cancer markers. Design: There were 26 Type-1 gNETs from 17 patients from our in-house surgical pathology service between 1997 and 2005. Basic demographic data were collected and patient charts were mined for evidence of metastatic disease or mortality. IHC was used to stain for Ki67, ER, and GATA-3.

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was readily identifiable in all but one case. Stornum fibrosis was a common feature. S-100 protein immunohistochemistry, performed on 11 cases, was reactive in all. Examples of submitted diagnoses on the 8 consultation cases included lymphoma, sarcoma, inflammatory myofibroblastic tumor, and sclerosing mesenteritis.

**Conclusions:** Rosai Dorfman disease is a rare inflammatory process that can occur in the gastrointestinal tract. Awareness of this very rare occurrence is important to avoid delayed diagnosis or confusion with a variety of neoplastic and non-neoplastic conditions.

### 813 Singapore Intestinal Metaplasia (SIM) Classification: MUC5AC Positive Immunophenotype and Multifocal Pattern Are Strong Predictors of Progression to Gastrointestinal Dysplasia

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**Background:** Intestinal metaplasia (IM) is a preneoplastic condition for gastric cancer (GC). The phenotypic pattern of mucin protein expression is altered in IM. Our aim was to identify subtypes of IM according to their pattern of mucin expression, their distribution in at-risk patients of GC in Singapore and to assess the IM subtypes which are associated with progression to GC.

**Design:** Endoscopic biopsies were obtained from Singapore Chinese subjects 50 years and above (n=2987), from 2004 till 2012, systematically reviewed by expert pathologists. Biopsies of 546 cases with moderate to marked IM were stained with Haematoxylin and Eosin, IHC/AB and immunohistochemistry was performed for MUC1, 2 and 5AC followed by quantitative staining analysis. Patients were followed up for a mean period of 46.6 months (range 0-88 months). Statistical analysis was performed and p-value <0.05 was considered significant.

**Results:** Progressed-to-dysplasia cases (IMD, n=9; EGC, n=15) from 546 patients. MUC1 expression was observed in 24.4%, MUC5AC in 43.4% and MUC2 in 100% cases. Based on H+/DAB and mucin expression, type IM I was seen in 53.5%, type II in 43.3% and type III in 1.1%. Type II IM was further subdivided into subtypes IIA (MUC1, 2, 5AC positive), IIB (MUC1, 2, 5AC positive), IIC (MUC1, 2, 5AC positive). MUC5AC and multifocal IM were significantly associated with progression to gastric dysplasia (p<0.05). Type III IM was associated with the highest rate of progression to dysplasia.

**First biopsy**

| Type | Dysplasia/carcinoma | Yes/No | OR | CI | p value |
|------|---------------------|--------|----|----|---------|
| Type I | 4 | 298 | Ref | Ref | Ref |
| Type IA | 8 | 87 | 6.85 | 2.01-23.29 | 0.002 |
| Type IB | 8 | 50 | 2.48 | 0.26-22.92 | 0.423 |
| Type IC | 9 | 100 | 7.70 | 2.02-22.24 | 0.002 |
| Type II | 3 | 6 | 24.83 | 3.78-162.73 | 0.001 |

Predictive power of combined MUC5AC expression and multifocal IM were higher than individual markers and clinicopathological features.

**Conclusions:** Incomplete IM (except type III) were significantly associated with the risk of progression to dysplasia/adenocarcinoma. Multiple biopsies should be evaluated in patients with IM to identify multifocal IM and MUC5AC expression could be helpful to assess the progression to gastric dysplasia or adenocarcinoma.

### 814 Loss of Switch/sucrose Nonfermenting Complex Protein Expression in Undifferentiated Gastrointestinal and Pancreatic Carcinomas

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**Background:** Undifferentiated carcinoma refers to an epithelial malignancy that lack morphologic evidence of differentiation. Recent studies have implicated the loss of constitutively expressed switch/sucrose nonfermenting (SWI/SNF) complex subunits in undifferentiated carcinomas of the gastrointestinal tract and the pancreas.

**Design:** We identified 22 cases of undifferentiated carcinoma found on resection from the gastrointestinal tract and the pancreas.

**Results:** Among the 15 review-confirmed undifferentiated carcinomas (7 colonic, 4 gastric, 3 pancreatic and 1 duodenal), 9 were pure undifferentiated carcinomas and 3 contained differentiated component with gland formation. All except one tumor were associated with advanced disease stage and 9 of 15 tumors were MMR protein-deficient. 2 tumors showed loss of BRG1 (1 with concurrent ARID1A loss) and 2 showed loss of INI1 (1 with concurrent ARID1A loss). 1 tumor showed concurrent ARID1A and ARID1B loss where ARID1A expression was absent in both differentiated and undifferentiated component while ARID1B expression was absent only in the undifferentiated component. 4 additional tumors showed loss of ARID1 only. BRG1, INI1 or ARID1B-deficient undifferentiated carcinomas consistently exhibited sheet-like growth pattern, with cellular discohesion and rhomboid morphology. In comparison, none of the 7 poorly differentiated carcinomas that were originally diagnosed as undifferentiated carcinomas showed loss of BRG1, INI1 or ARID1B.

**Conclusions:** Undifferentiated gastrointestinal/pancreatic carcinomas show frequent loss complex proteins. The loss of these key components of SWI/SNF complex may contribute to the arrest of cellular differentiation, resulting in the undifferentiated histology and aggressive clinical behavior.

### 815 Anal Canal Adenocarcinoma with Associated Perianal Paget’s Disease: An Underrecognized Entity with Institutional Experience

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**Background:** Anal canal adenocarcinoma(ACA) is a unique extraluminal cancer arising from anal mucosal glands that is particularly underrecognized both clinically and histopathologically. ACA is frequently misclassified as a colorectal or skin adnexal primary, due to its unusual location and ambiguous histopathology, especially when associated with extramammary perianal Paget’s disease (EMPDD). Reviewing our institutional archive indicates that ACA often presents a diagnostic dilemma due to its insidious nature and close association with EMPDD.

**Design:** We have encountered ACA cases that were initially misdiagnosed and furthermore, improperly managed as primary mucosal lesions. Twenty wide local excisions (WLE) of EMPDD, and one perianal excisional biopsy, coupled with radiologic and clinicopathological findings were retrieved and reviewed. Immunohistochemistry of cytokeratin 7 and 20, GCDP, GATA3, CDX2, CK5/6, P40 and P63 were performed. Next generation sequencing and analysis of mismatch repair proteins were carried out when an invasive process was identified.

**Results:** All 20 EMPDD cases were clinically believed to be intramuscular processes, due to unremarkable colonoscopic and radiologic studies. Upon review however, 2 of them showed invasive extramucosal ACA, composed of mucin, glands and signet ring cells, with a unique immunophenotype of CK7+/CK20+/CDX2+/GCDP+/GATA3+/P40+,-, identical to the EMPDD component. The remaining 18 EMPDD cases were confirmed to be mucosal-restricted processes only, with a distinct CK7+/CK20-/CDX2-/GCDP-/GATA3+ immunoprofile. Follow-up colonoscopies confirmed the absence of a gastrointestinal lesion in the 20 cases. The perianal excisional biopsy showed ACA only, with no EMPDD; however, it revealed inguinal lymph node metastasis. All 3 ACA patients underwent neoadjuvant therapies followed by a margin-free radical resection. Follow-ups at 20 months showed no recurrent disease.

**Conclusions:** A diagnosis of ACA should be entertained when facing any EMPDD, considering its insidious onset, poorly understood clinical course, and challenging management. Missing a diagnosis of ACA in an EMPDD patient could adversely impact the clinical course. Awareness of its immunohistochemical profile and deceptive EMPDD-like presentation may shed light on this infrequent, and yet significant entity.

### 816 Expect the Unexpected: Gastrointestinal Microsatellite Instable Adenocarcinoma without Characteristic Histopathological Features

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**Background:** Microsatellite instability (MSI) status in gastrointestinal adenocarcinoma impacts the clinical outcome of patients, as an important prognostic and predictive factor for response to conventional fluorouracil-based neoadjuvant treatment regimens. It has been widely accepted that MSI tumors display typical histomorphological characteristics such as rich mucin deposition, lymphocytic infiltration and muscular or signet ring morphology. However, our institutional review has identified frequent MSI tumors without these known microscopic features.

**Design:** We identified 307 colorectal and 53 small intestinal adenocarcinoma resection cases from 2012 to 2015. All cases were reviewed. The electronic chart, histopathology, immunohistochemistry and next generation sequencing (NGS) was analyzed and compared to published data findings associated with known MSI tumors.

**Results:** 68 of 307 (22.2%) colorectal and 8 of 53 small intestinal tumors displayed MSI, identified by immunohistochemistry. Histologically, 23 of the 68 (34%) colorectal MSI tumors showed no typical traits of MSI morphology; the average age of these 23 cases was 64.7 years with a male to female ratio of 0.8. Notably, 9 of these 23 (39%) involved non-right colon sites, mimicking microsatellite-stable (MSS) tumors. Immunohistochemistry revealed a loss of MLH1 and PMS2 in 14 (60%), MLH2 and MSH6 in 5 (21.7%), PMS2 in 3 (13.0%), and MLH1, PMS2 and MSH6 in 1 case (4.3%) among the 23 non-right sided MSI tumors.

In the 8 small intestinal MSI tumors, the average age was 57.4 years with a male to female ratio of 1.7, with 5 of 8 (62.5%) involving the duodenum, and 6 of 8 (75%) being adenocarcinomas. Histologically, 7 of the 8 cases were moderately to poorly differentiated and indistinguishable from their MSS counterparts. These cases demonstrated a loss of MLH1 and PMS2 in 4 (50%), MLH2 and MSH6 in 5 (21.7%), PMS2 in 3 (13.0%), and MLH1, PMS2 and MSH6 in 1 case (4.3%) among the 23 non-right sided MSI tumors.

**Conclusions:** Our investigation illustrates that more than one third of colorectal, and a majority of small intestinal MSI tumors do not display dependable histopathological features. In fact, MSI tumors may share a wide spectrum of both clinical and histomorphological features with MSS tumors. These findings encourage a more comprehensive approach to identifying MSI. Even in the absence of characteristic histological features, MSI testing should be uniformly performed to best guide effective and targeted therapeutic strategies.
Aneuploidy Detected by DNA Flow Cytometry Using Paraffin-Embedded Tissue Can Serve as Both Diagnostic Marker of Dysplasia and Predictive Marker of Neoplastic Progression in Inflammatory Bowel Disease
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Background: Distinction between regeneration and dysplasia, and between high grade dysplasia (HGD) and low grade dysplasia (LGD) can be challenging in inflammatory bowel disease (IBD), and reliable ancillary tests are not available. Flow cytometric analysis of DNA content (aneuploidy) has shown promise in stratifying IBD patients into low or high risk for colorectal cancer (CRC). These studies have typically used fresh tissue, which is not practical for integrating into the work flow, and does not allow direct correlation of flow cytometry results with follow-up findings. This study aims to evaluate if aneuploidy detected by flow cytometry using formalin-fixed paraffin-embedded (FFPE) tissue can aid in the diagnosis and risk stratification of dysplasia in IBD.

Design: DNA flow cytometry was performed using FFPE tissue from 18 flat HGD, 22 flat LGD, and 12 IBD without dysplasia. Three to four 60 micron thick sections were cut from each block, and area of interest was dissected for analysis.

Results: Aneuploidy was detected in 15 (83%) flat HGD, 9 (41%) flat LGD, and 1 IBD (8%) case without dysplasia. Forty-four percent of LGD cases with aneuploidy at baseline LGD was predictive of progression to HGD and/or CRC.

Aneuploidy

| No dysplasia (n=12) | Flat LGD (n=22) | Flat HGD (n=18) |
|---------------------|----------------|----------------|
| 1 (8%)              | 9 (41%)        | 15 (83%)       |

Progression to HGD or CRC at 1 year: 44% (with aneuploidy), 0% (without aneuploidy)

Conclusions: DNA flow cytometry using FFPE tissue can be helpful in establishing the diagnosis and risk stratification of dysplasia in IBD. The majority of HGD cases demonstrate aneuploidy, which can be helpful to confirm the diagnosis of HGD in challenging cases. The finding of DNA aneuploidy at baseline LGD is predictive of progression to HGD and/or CRC.

Tumor Buds and Micropapillae in Colorectal Carcinoma Demonstrate Similarities in Biological Behavior and May Represent Two Ends of the Same Spectrum
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Background: Micropapillary colorectal carcinoma (MC) has been reported as an aggressive variant of carcinoma associated with frequent lymphovascular invasion and poor outcome. The micropapillary components (MC) are clusters of closely adherent neoplastic cells, which are located in distinct empty spaces. While a single cell or clusters of up to 5 tumor cells were considered as a tumor bud, high tumor budding is also a hallmark of unfavorable tumor biology correlating with advanced tumor stage, lymphovascular invasion and metastasis. Micropapillary components (MC) and tumor budding (TB) are closely associated with favorable clinical outcome.

Results: 10 cases of colorectal carcinoma (CRC) with MC and 15 cases of CRC with high TB but without MC were included in this study. High tumor budding was based on histological examination. The micropapillary components (MC) were counted and calculated as percentage of Ki-67 positive cells out of total cells.

| TB cells of glandular component (400X) of MC/TB component and adjacent tumor cells of glandular component. For analysis of proliferation index (Ki-67), 3 high power fields were included in this study. High tumor budding was based on histological examination. The micropapillary components (MC) were counted and calculated as percentage of Ki-67 positive cells out of total cells.

Conclusions: MC/TB component and adjacent tumor cells of glandular component. For analysis of proliferation index (Ki-67), 3 high power fields were included in this study. High tumor budding was based on histological examination. The micropapillary components (MC) were counted and calculated as percentage of Ki-67 positive cells out of total cells.

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Conclusion: Our study demonstrates that high grade TB is often seen in CRC with MC. Both of the MC and TB component show increased GLUT-1 expression and decreased proliferation index. The reprogramming of glycogen metabolism by increased expression of GLUT-1 may help in providing nutrition to the MC and TB cells in a low proliferation state and aid aggressive biological behavior. This similarity in tumor biology, in addition to histology, may indicate that TB and MB are a part of the same spectrum.
822 Programmed Death-Ligand 1 Expression in Gastric Cancer: Correlation with Mismatch Repair Deficiency and HER2-Negative Status

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Background: Gastric cancer (GC) is one of the most common malignancies, especially in Asia. To date, many targeted therapies can only be benefited by the immune epidermal growth factor receptor 2 (HER2) positive patients. The immune regulatory programmed death-1 (PD-1) programmed death-ligand 1 (PD-L1) axis, which protects the host from overactive T-cells, has been used as an immune checkpoint target for immunotherapy in various malignancies. In colorectal cancer, it has been demonstrated that patients with mismatch repair (MMR) deficiency are good responders to anti-PD-1/PD-L1 immunotherapy. However, the indication of PD-L1 expression in GC remains controversial. The relationship between PD-L1 expression and the status of MMR proteins or HER2 expression needs to be understood profoundly.

Design: We retrospectively analyzed 571 consecutive cases of GC in our hospital from 2010 to 2012. PD-L1 and MMR protein were detected by immunohistochemistry (IHC). Positive PD-L1 expression was defined as at least 5% or more membranous and/or cytoplasmic staining in either tumor cells or tumor immune cells. HER2 status was assessed by IHC, and followed by fluorescence in situ hybridization in IHC 2+ cases.

Results: PD-L1 was identified in 17.0% (97/571) of GC. Deficient MMR (dMMR) could be detected in 48 patients (8.4%) in our cohort. GC with dMMR showed higher rates of PD-L1 expression compared with MMR proficient carcinoma (31.5%/VS15.7%, P=0.006). PD-L1 was positive in 15 of 33 cases (45.5%) without MLH1 and PMS2 expression (P=0.001), while only in 3 cases of 18 MSH6 negative cases (16.7%). For those 3 MSH2 negative cases, PD-L1 expression could not be detected. HER2 was positive in 61 (10.7%) cases, among which only three were positive for PD-L1 (4.9%). However, in HER2-negative group, 18.4% (94/510) of tumors were positive for PD-L1 (P=0.004). Univariate analysis showed that PD-L1 was a positive prognostic factor for disease free survival (DFS) (P=0.002) and overall survival (OS) (P=0.004). Moreover, when analyzing that showed PD-L1 expression was an independent predictor of DFS (P=0.013) and OS (P=0.004).

Conclusions: This study is the first evaluation of PD-L1 expression in a large Asian cohort of GC. PD-L1 is an independent positive prognostic factor and correlated with dMMR and HER2 negative status. Our finding indicated that MMR and HER-2 status may be potential biomarkers for anti-PD-L1 therapy.

823 Perianal Paget’s Disease: Experience of a Single Institution

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Background: The perianal Paget’s disease (PPDs) are the second most common location of extramammary Paget’s disease and can be associated with or without colorectal cancer. This study was designed to evaluate the immunophenotype and prognosis of PPDs.

Design: 23 patients with PPDs through tissue proved at the Taipei Veterans General Hospital during 2000 and 2015 were identified by a retrospective search of pathology records. Patient demographics, treatments, histopathological features, and long-term outcomes were documented. The expression of the CK7, CK20 and CDX2 of the PPDs by immunohistochemical (IHC) method is performed, and all slides were reviewed by two pathologists. The clinical and pathological stage of the CRCs and the outcomes were evaluated.

Results: Among the 23 PPD patients, 12 have concurrent CRC at the time of PPD diagnosis (8 anal canal, 4 rectal; 7 stage I or II, 4 stage III or IV, 1 unknown due to refusal of operation and further treatment). All cases are separated in four groups according to the concurrent CRC’s expression and expression of CDX2 in the PPDs: CRC+CDX2- (11 cases, 47.9%), CRC-CDX2- (case 4, 3.3%), CRC+CDX2+ (7 cases, 30.4%), and CRC-CDX2+ (1 case, 4.3%). The recurrent rate of CRC that developed in four patients was 25.0% (2/8) in stage I/II and 50.0% (2/4) for stage III/IV.

Conclusions: Our results reveal that CDX2 is a very useful antibody in differential diagnosis of PPD. Nodal negative CRCs with Paget’s disease had a much higher recurrent rate than same stage CRCs without Paget’s disease. Upstaging of these cases and more aggressive intervention such as adjuvant chemotherapy would be considered for these patients.

824 Taiwan Hospital-Based Detection of Microsatellite Instabilities and BRAF Mutation in Colorectal Cancer by Immunohistochemical Method

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Background: Microsatellite instability (MSI) plays an important role in colorectal carcinomas (CRCs), which would affect the chemotherapy administration, especially 5-fluorouracil-based adjuvant chemotherapy, in advanced stage cases. The microsatellite status evaluation could also be a screening tool for Lynch syndrome. DNA mismatch repair (MMR) proteins immunohistochemistry (IHC) facilitates universal screening of CRCs for microsatellite status: microsatellite stability (MSS) or microsatellite instability (MSI). The MMR proteins defect in CRCs of Taiwanese was investigated by the immunohistochemical method and this is a retrospective report of the experience in a medical institution in Taiwan.

Design: 439 patients with CRCs receiving coloscopy at the Taipei Veterans General Hospital in 2012 were identified by a retrospective search of pathology records. All slides were reviewed by two pathologists, and MMR status and BRAF V600E mutation detection by IHC are performed. Associations between MMR defect and patient’s stage and age were also evaluated.

Results: Among the 439 patients, 14 patients had been diagnosed with intramucosal adenocarcinoma in the polypectomy or mucosal resection specimen and there was no residual tumor in the coloscopy specimen. These patients were excluded and the residual 425 patients are involved. BRAF V600E polymerase chain reaction (PCR) and MMR IHC demonstrated the following phenotypes: BRAF-/MSS (391 cases, 92.0%), BRAF-/MSI (12, 2.8%), BRAF+/MSS (19, 2.1%) and BRAF+/MSI (13 cases, 3.1%). Among the 13 BRAF+MSI cases, 8 (61.5%) show loss of MLH1 and PMS2 expression, 3 (23.1%) show loss of MLH1 and PMS2, 6 (46.2%) show loss of MLH1, PMS2, MSH2 and MSH6 expression. One patient with loss of MLH1 and PMS2 expression has family history of CRC. Among advanced stage cases (stage III or IV), comparing the association between the microsatellite status (MSS or MSI) and the age (<70 years or ≤70 years), there is no statistically significant difference (p=0.10).

Conclusions: Our results reveal that the frequency of MSI of CRCs in Taiwanese is approximately 5.2%, while the frequency of BRAF+MSI cases is about 3.1%. BRAF+MSI is very useful in the screening for Lynch syndrome and the combination of IHC for MMR and BRAF should be considered in all stage and age groups for Lynch screening, treatment guidance and prognosis prediction.
SMAD4 staining was intact in the HG1. No statistically significant differences were found between the average age, grade, tumor size, or extent of invasion (p values) between tumors with and without SMAD4 loss. Cases with loss had a higher median nodal stage (p=0.048) with 68% having nodal metastases (vs. 47%). While not statistically significant, median survival was lower in patients with SMAD4 loss (12 vs. 20 months, p=0.41), and they were more likely to survive 5 years (10% vs. 27%, p=0.13) and ≥10 years (0% vs. 17%, p=0.10).

Conclusions: A subset of EACs lacks SMAD4 immunohistochemistry indicating that, in addition to pancreas, an esophageal primary needs to be excluded in metastases of unknown primary with SMAD4 loss. The increased proportion of loss in cases compared to the prior report may reflect a different population and that our cases were collected at an earlier timepoint with different protocols for resection and neoadjuvant therapy. We did not see SMAD4 loss in precursor lesions supporting the hypothesis that SMAD4 mutations are a late event in EAC tumorigenesis. While not statistically significant, our data directionally support prior data showing that SMAD4 mutations indicate a worse prognosis.

Goblet Cell Carcinoid: Distinct Profile Compared to Neuroendocrine Tumor and Colorectal Adenocarcinoma
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Background: Goblet cell carcinoid (GCC) is a rare appendiceal tumor and can have an additional adenocarcinoma (AC) component. Both GCC and GCC-AC are staged and treated like AC. The word “carcinoid” in GCC frequently leads to confusion with colorectal carcinoids. This study examines the genomic landscapes of appendiceal NET, GCC and GCC-AC.

Methods: Capture-based next generation sequencing (NGS) targeting the coding regions of 479 cancer genes and select introns was performed. Somatic single nucleotide variants (SNVs), insertions/ deletions (indels), copy number alterations (CNAs), and selected rearrangements were evaluated.

Results: Coding mutations were not seen in any NET, but were present in all GCC and GCC-AC cases (average 5.3). Mutations in chromatin remodeling genes were seen in all GCC-AC cases (ARID1A: 2 cases; KMT2A: 1 case; KMT2B: 1 case; KMT2D: 1 case; KDM6A: 1 case). SOX9 frameshift mutations (transcription factor involved in development of intestinal epithelium) were present in 2 GCC-AC cases (2 separate frameshift mutations in 1 case). 1 mutation in Btg2 (Ras homolog gene family, member A; a small GTPase protein of Rho family) was seen in 1 GCC-AC case and 1 mutation in TP53 in another. A single pure AC case showed mutations in APC, KRAS, and TP53. Mutations in APC, KRAS, PIK3CA, SMAD4, or pathogenic germline alterations were not identified in any other cases.

Conclusions: The mutational profile of GCC/GCC-AC is distinct from NET, and does not show mutations commonly observed in colorectal cancer including APC, KRAS, PIK3CA, SMAD4, or TP53. Mutations in SOX9 and chromatin-modifier genes (ARID1A, CDH1, KMT2D, KDM6A) may play an important role in GCC and GCC-AC.

Immune Infiltrates Confer Prolonged Survival in Colorectal Cancer with Microsatellite Instability
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Background: Microsatellite instability (MSI) occurs in about 15% of colorectal cancers (CRC), and confers a good prognosis. Several potentially prognostic pathological features are commonly associated with MSI CRC, including immune infiltrates, high grade, mucinous or signet ring differentiation, and BRAF mutation. We hypothesized that the presence of immune infiltrates is the main factor that confers prolonged survival in MSI CRC.

Methods: A series of 938 colorectal cancers were reviewed, enriched for cases with confirmed MSI, or with pathological features common to MSI tumors (high grade, mucinous differentiation, BRAF mutation). Tumour infiltrating lymphocytes (TILs) were scored in each tumor by a semi-quantitative measure per 5 high power fields (0.55mm field diameter). Cohnheim infiltrates beyond the invasive front were scored as lymphoid aggregates per low power field (5mm field diameter). Cases were also reviewed for conventional prognostic factors.

Results: MSI CRC was significantly associated with of origin in the proximal colon, female gender, mucinous differentiation, BRAF mutations, TILs and Cohnheim infiltrates (p=0.05), consistent with previous reports. MSI CRC had a significantly lower incidence of stage 4 disease relative to MSS CRC (p=0.05). In stage matched disease there was no difference in overall and relapse-free survival, but the presence of TILs or Cohnheim infiltrates were independently associated with prolonged survival in AJCC stage 3 MSI CRC.

Conclusions: Lymphocyte infiltrates are prognostic for a more favourable outcome in colorectal cancers with microsatellite instability. A subset of MSI CRC's lack immune infiltrates; it is not clear if this finding in the context of other potential poor prognostic factors will be discussed.

Prognostic Impact of Grade and MSI Status in Muscular Colorectal Cancers
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Background: Muscular colorectal carcinoma (mCRC) and mucin-producing colorectal carcinoma (mpCRC) are defined as tumors with >50% and >50% mucin differentiation respectively. WHO guidelines recommend that conventional grading should not be applied to mCRC, but that MSI status should be used to stratify risk in these tumours. We aimed to assess the validity of these guidelines in predicting the clinical behaviour of mCRC and mpCRC.

Design: A series of 951 colorectal cancers was reviewed, enriched for cases with reported MSI status. We reviewed for presence and extent of mucin differentiation, classified as mCRC, mpCRC and non-mucinous CRC. WHO grading was applied to all tumours; in mucin fields, strips of epithelium at the periphery of mucin lakes with retained nuclear polarity were regarded as low grade, whereas solid cancer nests were regarded as high grade. Cases were also assessed for conventional prognostic factors, and for BRAF and MSI status. Relapse-free survival and overall survival were assessed in univariate and multivariate analyses.

Results: Both mCRC and mpCRC were significantly associated with origin in the proximal colon, female gender, MSI, BRAF mutation, increased tumour infiltrating lymphocytes and less venous invasion (p<0.05). There was no significant difference in these features between mCRC and mpCRC, and there was no difference in patient outcomes. High grade conferred a poor prognosis in both mucinous and non-mucinous colorectal cancer. MSI was a good prognostic factor in mCRC/mpCRC in univariate analysis, but not in multivariate analysis. Lymphocyte infiltrates were a better predictor of survival than MSI status.

Conclusions: mCRC and mpCRC have similar clinicopathological and molecular features. The arbitrary distinction between mCRC and mpCRC appears to have no biological or prognostic value. Assessment of grade was found to be prognostic despite current guidelines to the contrary. MSI status may play a role in determining prognosis, but this is likely due to the increased likelihood of lymphocyte infiltrates.

Alterations in Lamina Propria and Muscularis Mucosa in Ulcerative Colitis Are Associated with Prior Medication and Degree of Histologic Inflammatory Activity
Eric Wilts, Rocio Lopez, Neha Agrawal, Florian Biedert, Illyssa Gordon. Cleveland Clinic, Cleveland, OH.

Background: Ulcerative colitis has classically been described as a mucosal disease, as compared to its counterpart Crohn’s disease, which is transmural. Although it is known that ulcerative colitis affects the superficial mucosa, the range of histologic patterns that can be seen in chronic disease has not been described. Here we investigate changes to the lamina propria and muscularis mucosa that can be seen in ulcerative colitis. Current guidelines to the contrary. MSI status may play a role in determining prognosis, but this is likely due to the increased likelihood of lymphocyte infiltrates.

Design: Diagnostic H&E stained sections taken approximately every 10 cm from 94 consecutive colectomy specimens for ulcerative colitis were reviewed and assessed for the presence of lamina propria fibrosis and for qualitative alterations in the muscularis mucosa, including uniform thickening, splitting, splaying, thickening, and lamina propria which are related to prior medication use and to the degree of histologic inflammatory activity. Clinical characteristics were also collected.

Results: In ulcerative colitis, there was a band pattern of lamina propria fibrosis and associated prominent lymphocyte infiltrates; the significance of this finding in the context of other potential poor prognostic factors will be discussed.

Altered Expression of Lamina Propria Tissue Markers in Ulcerative Colitis Are Associated with Prior Medication and Degree of Histologic Inflammatory Activity
Eric Wilts, Rocio Lopez, Neha Agrawal, Florian Biedert, Illyssa Gordon. Cleveland Clinic, Cleveland, OH.

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Results: In ulcerative colitis, there was a band pattern of lamina propria fibrosis and associated prominent lymphocyte infiltrates; the significance of this finding in the context of other potential poor prognostic factors will be discussed.
Introduction: The pathogenic relationship between chronic inflammatory bowel disease (IBD) and colorectal neoplasia is ill defined, as these cases are rare. The findings are variable in multiple studies regarding the rate of NEPs in IBD, as well as the role of inflammation in the development of NEPs in IBD. This study investigates clinical and pathologic features to identify a discrete profile of features that could contribute to understanding the biology of NEPs in IBD.

Design: We identified a cohort of patients with IBD and colorectal adenocarcinomas. The institutional surgical pathology archives were searched to identify cases with both IBD and NEPs. Poorly differentiated neuroendocrine neoplasms were excluded. Glass slides, with associated immunohistochemical stains, were reviewed to investigate the pathologic features. Clinical, radiological, and laboratory findings were also reviewed via institutional electronic medical records.

Results: Twelve cases (median age 32, range 18-62; M:F=7:5) were identified from a total of 3151 IBD cases from 1994-2016; including ulcerative colitis (n=6), Crohn’s disease (n=5), and indeterminate (n=1). In all 12 cases, NEPs were incidentally discovered. Three cases were classified as endocrine cell micronests (ECMs)(each ≤ 0.5 mm). The 9 remaining cases were well-differentiated neuroendocrine tumors (NETs) that were further classified into micrometastases (median size 2.0 mm, range 1.0 - 3.0 mm) and carcinoids (median size 8.0 mm, range 5.0 - 11.0 mm). Inflammation was identified in adjacent mucosa in 100% of ECMs and 66.7% of NETs. NECs occurred in the rectum (n=6), appendix (n=3), rectosigmoid (n=2), and rectum (n=1). Four cases exhibited mucosal neuroendocrine cell hyperplasia adjacent to ECMs and NETs. There was no progression of ECMs or NETs at a median follow-up of 5 years (range 2-31 years).

Conclusions: Compared to the rate of NEPs in the SEER database, IBD patients in our institution 5 years more likely to have NECs of 5.5% than the general population. These findings suggest that NECs may develop in patients with IBD, which has not been previously noted. Further studies are needed to determine the role of inflammation in the development of NECs in IBD.

Background: Medullary carcinomas of the colon (MC) are a rare colorectal carcinoma subset with a favorable prognosis despite its undifferentiated morphology. MCs (Figure 1), including PD CRC. GPA33 stained more MCs than all other markers, including the novel IHC marker, GPA33. Although recent studies have suggested that GPA33 and CDH17 and SATB2 may be reliable markers for MC, our data is less supportive. GPA33 is a cell surface antigen that is expressed in normal colonic epithelium.

Conclusions: In this large cohort (n = 99) of MCs we found decreased expression of intestinal markers, including the novel IHC marker, GPA33. Although recent studies suggest that CDH17 and SATB2 may be reliable markers for MC, our data is less supportive. MCs were more often positive for GPA33 than for the other markers of intestinal differentiation, staining 32% of MCs that were negative for all other markers. GPA33 may be a helpful marker to determine intestinal differentiation in poorly differentiated and medullary colorectal carcinomas.

Results: In the CRC tissue microarray specimens, normal adjacent tissue (NAT) (n=52) had a mean TMIGD1 staining score of 1.87, and grade 1 (n=21), 2 (n=62) and 3 (n=29) tumors had mean scores of 2.24, 1.32 and 1.14, respectively. Expression of TMIGD1 was significantly higher in both NAT and well differentiated grade 1 tumors than in grade 3 tumors (P<0.01). Additionally, we have identified an approximately 100 base pair sequence on the 5’ flanking end of the TMIGD1 promoter involved in the regulation of TMIGD1 expression.

Conclusions: TMIGD1 is expressed in human colonic epithelial cells. There is an inverse correlation between TMIGD1 expression and the grade of CRC. TMIGD1 expression was relatively high in both NAT and well-differentiated CRC, however, it was significantly reduced in poorly differentiated advanced CRC. Promoter analysis demonstrated that the presence of a 100 base pair sequence on the TMIGD1 promoter is required for expression. TMIGD1 is a potential biomarker in advanced CRC.
835 KRAS and VEGF Gene 3′-UTR Single Nucleotide Polymorphisms Predicted Susceptibility in Colorectal Cancer
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Background: Single nucleotide polymorphisms (SNPs) in tumor-related genes have been reported to play important roles in cancer development. Recent studies have showed that 3′-UTR polymorphisms are associated with the occurrence and prognosis of cancers. The aim of this study is to analyze the association between KRAS and VEGF 3′-UTR SNPs and genetic susceptibility of colorectal cancer (CRC).

Design: In this case-control study of 371 CRC cases and 246 healthy controls, we analyzed the association between one SNP (rs1137188G > A) in the KRAS gene and four SNPs (rs10434A > G, rs3025034C > T, rs3025034G > A, rs3025035G > A) in the VEGF gene and CRC susceptibility by the improved multiplex ligase detection reaction (iMLDR) method. We checked the selected SNPs’ minor allele frequency and its distribution in the frequency of Chinese people by Hapmap database and Hardy-Weinberg equilibrium, and used multivariate logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs).

Results: We found that only the rs3025035C variant genotype in the VEGF gene was associated with a significant protection for CRC (adjusted OR = 0.696, 95% CI = 0.489 - 0.992; p = 0.044 for CC and CT- TT). However, these were not found for the other SNPs (rs1137188G, rs3025034A and rs10434A A). In genetic polymorphisms analysis, we found that the KRAS rs1137188 variant AA genotype was more evident in colon and had higher portion of tumor size ≥ 5 cm, and suggested that the rs1137188 variant AA was associated with significantly increased risk of CRC (P = 0.05). The rs3025039 variant CC genotype was more evident in colon, tumor size < 5 cm and clinical stages III and IV.

Conclusions: Our study suggested that KRAS rs1137188 and VEGF rs3025035 may predispose patients to CRC and they may play important roles in the development of CRC.

836 Patterns of Injury in Esophageal Candidiasis: Clinical, Endoscopic, and Pathologic Correlations
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Background: Candidiasis is the most frequent cause of infectious esophagitis which may be seen in immunosuppressed (IS) as well as immunocompetent (IC) patients. Plaques and patchy or diffuse exudates are the characteristic endoscopic findings. We have noted a wide range of patterns in biopsies obtained from patients with Candida esophagitis, and performed this study to determine whether they correlate with clinical features, endoscopic findings, and immune status of the patients.

Design: We reviewed 70 consecutive esophageal biopsies that contained Candida. Each biopsy was assessed for the presence and type of inflammatory reaction and classified as non-inflammatory and inflammatory; the distribution and type of inflammation was noted in the latter group. Histologic findings were correlated with clinical features, endoscopic appearance and immune status of patients. A Fisher exact test was used for statistical analysis.

Results: All of the study patients were adults (mean age 56 years, M/F = 5/9). Thirty-two (40%) were IS due to HIV/AIDS (n = 5), chemotherapy (n = 13), and immunosuppressive treatment (n = 14). Endoscopic abnormalities were noted in 35 (50%) patients. Seventeen (24%) had plaques with parakeratosis, invasive fungi and keratin debris, but no inflammation. Nine (3%) were IS. Within this group, Candidiasis was endoscopically suspected in similar numbers of IS and IC patients. Most biopsies with histologic inflammation contained superficially oriented neutrophils (34, 49%), 15 (21%) had, in addition, numerous lymphocytes, and 4 (6%) only lymphocyte. Histologic inflammation correlated with endoscopic evidence of candidiasis in 60% IC individuals, but only 26% of IS patients (p = 0.02). Interestingly, four patients with a lymphocyte-predominant infiltrate had achalasia (n = 2) or scleroderma (n = 2).

Conclusions: Classic endoscopic features of candidal esophagitis are present approximately 50% of all patients but only in 26% of IS patients with histologic inflammation. In addition to the well-known neutrophil-rich inflammation, abundant intraepithelial lymphocytes may be present. The latter inflammatory pattern was seen in patients with dysmotility disorders. Nearly 25% of cases lack mucosal inflammation but showed parakeratosis, invasive fungi, and detached debris containing fungi. No correlation was found between these inflammatory / reactive patterns and the immune status of the patients.

837 PD-L1 Expression in DNA Mismatch-Repair-Deficient and Medullary-Type Ampullary Carcinomas
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Background: Programmed death-ligand 1 (PD-L1) expression by tumors is a mechanism by which tumors can evade the immune response and therefore this pathway is a target for immunotherapy. Since colorectal carcinomas with microsatellite instability preferentially express PD-L1 (PMID: 27198569), we investigated PD-L1 expression in mismatch-repair-deficient (MMR-D) and medullary-type ampullary carcinomas (AC).

Results: PD-L1 expression was seen in 6 of 8 medullary carcinomas (4 of which also had MMR-D) but none of the 19 non-medullary MMR-D carcinomas showed PD-L1 positivity (p = 0.001). The PD-L1 expresser carcinomas (PD-L1 +ve) had the following characteristics as opposed to PD-L1 negative (PD-L1 -ve) group: larger invasive size (6 cm vs 2.3 cm, p = 0.04), BRAF mutation (p = 0.02), and tumor acini expressing PD-L1 (p = 0.001). PD-L1 +ve AC were also associated with tumor budding and poor prognosis (1,3, 3-year survival of PD-L1 +ve vs PD-L1 -ve: 75%, 75% vs 94%, 88%, respectively) although this did not reach statistical significance (p = 0.08 and p = 0.79 respectively).

Conclusions: PD-L1 expression is seen in 75% of medullary carcinomas (many of which are MMR-D) as well but not in non-medullary MMR-D AC. As such, PD-L1 expression is associated with increased tumor-infiltrating lymphocytes, larger invasive size, and BRAF mutation. Accordingly, ACs of medullary type ought to be considered as potential candidates for PD-1/PD-L1 immunotherapy.

838 Duodenal Neoplasms of Gastric Phenotype: An Immunohistochemical and Genetic Study with a Practical Approach to the Classification
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Background: Duodenal neoplasms of gastric phenotype (DNGP) is very rare, and details of histopathological, genetic and biological pathways are still not clear. Genetic studies in GNAS, KRAS and APC have been reported in pyloric gland adenoma and fundic gland type neoplasm of the stomach.

Design: In this study, we encountered 16 cases of extra-ampullary DNGP from benign to malignant, and examined mucin immunoprofile and oncogenes mutations (GNAS, KRAS, APC, BRF and CTNNB1).

Results: The 16 DNGPs were histologically classified into 7 adenomas (5 pyloric gland adenomas and 2 foveolar-type adenomas), 6 neoplasms of uncertain malignant potential (UMC) and 3 invasive adenocarcinomas (AC). Eight (50%) cases had GNAS mutations, including in 6/16 cases (38%) of DNGP [4/7 (57%) adenomas, 1/6 (16%) UMC, 1/3 (33%) invasive adenocarcinomas] and APC in 4/15 (27%) DNGPs [0/7 (0%) adenomas, 2/3 (67%) UMCs, 2/3 (67%) invasive adenocarcinomas]. BRAF mutation was present in only one (16%) UMC, and KRAS or CTNNB1 mutation was absent.

Conclusions: In conclusion, gastric-phenotypic adenoma and UMC of the duodenum are similar to each counterpart of the stomach in terms of histological, genetic and clinicopathological features. We would like to propose a term of NUMP as an intermediate category between adenoma and invasive adenocarcinoma. Our results may provide novel insights into the classification of unclassified duodenal tumors showing analogy with gastric phenotypic neoplasms of the stomach.

839 Diagnostic Utility of SATB2 in Gastrointestinal Poorly Differentiated Adenocarcinomas with Signet Ring Cells, Pure Signet Ring Cell Carcinomas and Goblet Cell Carcinoids
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Background: SATB2 has been shown to be a sensitive diagnostic marker for colorectal adenocarcinomas (CRAs). However, reported studies focused only on glandular-forming CRAs and no study has tested SATB2 in gastrointestinal poorly differentiated adenocarcinomas with signet ring cell feature (PDA-SRCs), pure signet ring cell carcinomas (PSCRs) and goblet cell carcinoids (GCCs). Here we investigated SATB2 immunoreactivity in these tumors and compared its diagnostic utility to CDX2.
ANNUAL MEETING ABSTRACTS

840 Morphological and Molecular Features of Gastric Glomus Tumors
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Design: We analyzed six cases of GGTs resected between 2000 and 2016. Clinicopathological features were reviewed and immunohistochemical studies were performed. Next generation sequencing (NGS) was done in three cases to screen for mutations in a panel of 467 cancer-related genes in the Columbia University Comprehensive Cancer panel (CCCP). Tissue macrodissection was performed to enrich for tumor tissue (at least 80%) for DNA extraction. All 6 cases were tested for BRAFV600E and KRAS exon 2 mutations by PCR and Sanger sequencing.

Results: The mean age of the 6 patients was 57.3 years (range: 45-72), with a male predominance (4 males and 2 females). All tumors occurred in the distal stomach. The mean depth across various amplicons is 2,000×, and non-synonymous SNVs were obtained from the Pathology report and medical record. NGS was done on The Ion MG Kit and sequenced on the Ion S5 platform. The absence of L1CAM staining in 4 of the 11 cases confirms the need to profile the tumor tissue to identify potential non-responders.

Conclusions: SATB2 was positive in the upper GI PDA-SCRs/PSCRs. In colorectal PDA-SCRs and PSCRs, SATB2 was not as sensitive as CDX2 and showed decreased immunoreactivity with decreasing differentiation. SATB2 showed similar high sensitivity as CDX2 in goblet cell carcinoids.

841 Profiling of Metastatic Colorectal Cancers Identifies Potential Responders to Targeted Therapy
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Background: Metastasis of colorectal adenocarcinoma (CRC) is a problem that affects approximately half of the patients with the disease and this needs to be addressed. In advances of the field, antibody drug conjugate (ADC) therapy may be a promising approach in that directed therapy can be administered to specifically target metastatic tumor cells. ADCs are comprised of a monoclonal antibody linked to a toxic carrier payload. There are a number of ADCs that have either been recently introduced to the clinic, are in clinical trials, or in development. Refining their use requires identifying targets in study, a panel of antibodies of both monoclonal antibodies (mAb) or protein (PMab) which have been reported to be expressed more in tumor cells than normal cells were tested on cases of metastatic CRC to determine the utility of a profiling approach to differential presentation potential responders to ADC based adjuvant therapy.

Design: Eleven cases of CRC were identified and blocks consisting of lymph nodes with metastatic disease were tested against a panel consisting of five antibodies (PTK-7, Trop-2, AXL, CD12, and LICAM) directed to these PMbPs. Antigen retrieval using an autostainer and conventional immunohistochemical methods were performed to optimize conditions and later test on the tissue sections. The resulting stained slides were evaluated to determine plasma membrane expression (PMbE). A case was considered positive if >25% of the tumor cell population demonstrated PMbE.

Results: SATB2 was positive in 18/26 SATB2-positive colorectal ADCs, SATB2 staining was lost in the SRC component but retained in the non-SRC component in 7 (39%), less SATB2 positivity in the SRC component than the non-SRC component in 6 (33%), similar SATB2 positivity in the SRC and non-SRC components in 5 (28%). SATB2 and CDX2 were both positive in 2/3 appendiceal ADC. All 17 appendiceal GCCs were positive for both SATB2 and CDX2. Detailed comparison of SATB2 to CDX2 was summarized in Table 1.
Results: Strictures were characterized by a mean 2.3-fold increase in overall mural thickness and by a 2.6- and 1.8-fold increase in the areas occupied by smooth muscle and collagen, respectively. Approximately half the increase in wall thickness was attributable to a mean 22-fold expansion of the muscularis mucosae (MM) from 2.2±1.6% to 16.5±10.1% of the total mural thickness and the remainder of the increase to expansions of the internal layer of muscularis propria (MP-I) and submucosa (SM). The external layer of the muscularis propria was similar in thickness and composition to controls. Microscopically, the expanded MM featured (1) architectural disarray, (2) myocyte hyperplasia and (3) pericellular collagen fibers. In contrast, the thickened MP-I featured (1) preserved muscular architecture, (2) no pericellular collagen fibers, and (3) widened intramuscular septa with increased collagen. The SM exhibited fibrosis in continuity with the intramuscular septa. Additionally, submucosal arteries and veins frequently exhibited eccentric fibromuscular hyperplasia which was polarized toward the mucosa.

Conclusions: Strictures in Crohn’s ileitis is characterized by distinctive fibromuscular alterations in the individual intestinal wall layers. These alterations may reflect differential mesenchymal responses to luminal-based and transmural inflammatory stimuli. The implications for stricture pathogenesis may help guide progress toward prevention and therapy.

844 Constrictive Strictures in Crohn’s Ileitis
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Background: Ileal strictures in Crohn’s disease (CD) classically present as segmental regions of mural thickening, “rubber-hose” rigidity and luminal narrowing, features that correspond microscopically to fibromuscular, lymphoid or neural hypertrophy and distorted mural architecture. We describe a subset of ileal CD strictures in which these features are relatively inconspicuous and where luminal narrowing results mostly from contractions of the intestinal wall.

Design: In a prospective study, resected ileal strictures of 26 CD patients were serially sectioned along with the adjoining non-strictured bowel. Evaluation of HE-stained slides revealed a subset of strictures with reduced external circumference. For morphometric analysis we selected a specimen that contained 5 separate strictures yielding a total of 79 cross-sections (Figure). HE and smooth muscle actin-stained slides were digitally scanned at 20X and evaluated morphometrically via Halo software (Indica Labs).

Results: The outer circumferences of the intestinal wall in strictured segments at their narrowest points measured 58.1, 72.1, 63.0, 69.4, and 66.2% of controls. The walls of the strictured segments and individual muscular layers were thickened compared to control segments (mean 6.4±2.2 vs 3.6±0.9mm, respectively, p<0.004) but there were no significant differences in the areas of the muscularis mucosae (11.3±2.0 vs. 14.3±7.2mm², respectively, p=0.77) or muscularis propria (75.1±10.0 vs. 65.1±1.7mm², respectively, p=0.69), suggesting a net conservation of muscle mass. There was no histological evidence of architectural distortion of the mural layers or substantial neural or lymphoid hyperplasia. The maximal proportions of outer circumferences covered by mesenteric fat in the strictured and non-strictured areas were 79.8±5.6% vs. 42.5±4.9%, respectively (p=0.004).

Conclusions: A subset of “constrictive” ileal strictures in CD is characterized by contracture, preserved mural architecture and near-encasement by mesenteric fat. We hypothesize that such strictures result from compression by hypertrophic mesentery, but cannot exclude a role for unidentified physiologic interactions between the mesentery and intestinal wall. These findings support recent hypotheses regarding a primary role for the mesentery in the pathogenesis of CD.

845 PTEN and p27 Loss Differ Among Morphologic Patterns of Prostate Cancer
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Background: The presence and amount of cribriform prostate cancer (Crbr.) versus other Gleason 4 cancer are associated with increased recurrence (PMID:21685037) and cancer death (PMID:25189638). PTEN loss inactivates cell cycle inhibitor p27/ Kip1. (PMID:11175795): both prognostically adverse events, whose correlation with morphology has not been studied in detail.

Design: Selected whole slides from 46 cancer specimens with Cribr. were immunostained (IHC) for PTEN or p27. A subset of 15 cases was studied by chromogenic in situ hybridization (ISH, RNAscope®; Advanced Cell Diag.) using probe to PTEN or CDKN1B (to detect p27). To analyze both IHC and ISH, for each Gleason (Gl.) morphologic subtype, 2-3 JPG 400x images were captured, and (after editing out stroma) the fraction of tumor epithelium positive was digitally assessed using Axiosvision Release 4.7.1. For IHC, 0-6.1 was assigned 0, >0-1.0-4.0 was 1+, >0-4.0-7.3 was 2+, >0-7.3 was 3+. Statistical analysis for IHC used the Kolmogorov-Smirnov test (10 comparisons, significant if p<0.005). ISH used fixed effects for morphology and random effects for each patient (significant if p<0.05).

Results: IHC

| Acini | Mean PTEN IHC (0-3+) | p   |
|-------|---------------------|-----|
| Benign| 2.52                | ref |
| Gl. 3 | 1.88                | 07  |
| Gl. 4- Fused | 1.50          | .0012|
| Gl. 4 Cribr- peripheral cells | 1.48 | .01 (borderline) |
| Gl. 4 Cribr- central cells | 0.90 | <.0001 |
| Gl. 4 Cribr- small size like benign | 1.22 | .003 |
| Gl. 5 | 0.80                | <.001|

p27 loss compared to benign acini (mean 2.5+) was significant only for Cribr- peripheral (mean 1.5+, p=.0029); Fused was (p=.0075).

ISH: With PTEN, significant loss normalized to benign acini was observed for cribriform cancer (p<0.02), but not for fused small acini or Gleason 3/4/5/6 acini.

Conclusions: PTEN and p27 loss are differentially distributed among morphologic patterns of prostate cancer. Cribriform structures’ peripheral cells have higher proliferation index according to prior work. PTEN loss predominates in central cells and p27 loss peripherally, suggesting that a high proportion in the proliferation plays a role in generating cribriform growth. For PTEN loss as a prognostic factor, cribriform structures demand separate assessment in peripheral vs. central populations.

846 Non-Tumoral Parenchymal Changes in Renal Cell Carcinoma Cases
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Background: Large, unexplained geographical variations in renal cell carcinoma (RCC) incidence rates have been observed, with the highest rates observed in the Czech Republic (CR). We explored chronic pathological changes in the non-tumoral renal cortex (CPCR) of RCC cases from five European countries involved in the Cancer Genomic of the Kidney (CAGEKID) study, and their possible relationship with tumorigenesis.

Design: Scanned images of 626 frozen normal tissue samples distant from the tumor in conventional RCC cases from CR, Romania, Serbia, United Kingdom (UK) and Russia were read twice by one pathologist who evaluated the degrees of interstitial inflammation and fibrosis, tubular atrophy, glomerulosclerosis and arterial wall thickening. In the CAGEKID project, an independent systematic review of normal tissues was conducted by another pathologist to assess the level of inflammation and fibrosis with additional comments for any other specific features such as glomerulosclerosis. The agreement between these two independent observations was 89%. We used logistic regressions to analyze the association of these pathological with clinico-pathological variables and country of residence.

Results: CPCR were observed in 116 (18.5%) of samples. Higher age was the strongest predictor (OR=1.86 for 1-year increment, 95% CI: 1.04-1.88). After adjusting for age, country was significantly associated with the presence of CPCR. Compared to Russia, CPCR were more common in CR (OR=2.94, 1.15-7.61) and in Romania (OR=3.56, 1.80-7.07), while no significant difference was observed with the UK and Serbia. To assess potential confounders of the association with country and sampling method, we