Su2030
Pre-Treatment Neutrophil, Lymphocyte and Platelet Counts in Mismatch Repair Deficient Colorectal Cancer
Shahroze Rashash, Xiaoyan Ruan, Ruth Johnson, Brooke R. Druliner, Donna Felmelee Devine, Lisa A. Boardman

Background: Mismatch repair deficiency status (d-MMR) in colorectal cancer (CRC) is defined by the absence of the proteins involved in the repair of mismatched DNA. Lack of staining for the (MMR) proteins (MLH1, MSH2, MSH6, PMS2) on immunohistochemistry studies is characteristic of d-MMR tumors. MMR deficiency results in increased mutation rate and micro-satellite instability (MSI) of the cancer cell genomes. Histologically d-MMR tumors present with increased inflammatory infiltrate suggestive of immunoreactivity of these cancer cells. Additionally recent studies have shown that these tumors are more responsive to immunotherapy. Understanding the inflammatory response evoked by a d-MMR tumors, potentially reflected on the peripheral white blood cell counts, may provide benefit in regards to further evaluation and potentially recognizing candidates for immune therapy. In this study we aim to compare the pretreatment inflammatory cell counts of patients with d-MMR tumors to those with MMR proficiency (p-MMR) state. Methods: Immunohistochemistry studies for MMR protein staining of all the patients with CRC who were seen at the Mayo Clinic, Rochester, MN, from 2004 to 2015 were reviewed. Data including tumor stage, leukocyte counts and differentials within 30 days prior to surgery or initiation of chemotherapy were obtained. Absolute neutrophil, lymphocyte and platelet counts were compared between patients with d-MMR and p-MMR CRC. Results: 114 patients with d-MMR tumors were compared to 442 patients with p-MMR status. The average neutrophil count was noted to be 0.9 (x 10^9/Liter) higher in d-MMR status patients (P < 0.0001). The average platelet count was also found to be greater by 38.0 (x 10^9/Liter) in MMR deficiency state (P = 0.0001). The difference in the average lymphocyte count and neutrophil to lymphocyte ratio (NLR) did not reach statistical significance. When adjusted for the disease stage the difference in the platelet counts remained significant for stage one through three. Neutrophil counts remained significantly elevated for stage two and three d-MMR tumors. For stage 1 tumor, there was a trend in the mean neutrophil count difference between the two groups, but this did not reach statistical significance. There was no difference in NLR based on MMR status across all stages. Conclusion: In this study d-MMR tumor status was associated with higher neutrophil and platelet counts in the peripheral blood of patients with CRC. This is suggestive of an acute phase reaction in response to tumor cells in earlier stage disease potentially induced by immunogenic MSI cancer cells. If further validated the findings of this study may be leveraged to identify potentially immunogenic tumors responsive to immunotherapy.

Su2031
Methionyl-tRNA synthetase Serves as a New Prognostic Marker in Pancreatic Cancer
Yi-Yong Baek, Sung Ill Jang, Su Yoon Lee, Joen Seong Park, Dong Sup Yoon, Chang Moo Yi

Objective: Methionyl-tRNA synthetase (MRS) is frequently upregulated in PDAC tissue compared with normal pancreatic tissue. Overexpression of MRS in several different types of cancers, such as malignant fibrous histiocytomas, sarcomas, malignant gliomas and glioblastomas. However, MRS expression pattern and biological behavior in pancreatic ductal adenocarcinomas (PDAC) remains completely unclear. The present study is designed to investigate the clinical and prognostic value of MRS in PDAC, and to further identify its role as a potential tumor marker and therapeutic target of PDAC.

Patients and methods: A total of 111 surgical samples were collected from Gangnam Severance Hospital and Yonsei Severance Hospital between 2012 and 2013. Serial sections of paraffin embedded pancreatic tissues from 70 patients diagnosed with pancreatic ductal adenocarcinoma (PDAC) and 41 control patients were assessed for expression of MRS using immunohistochemistry (IHC). IHC score was based upon the product of the percentage of MRS positive cells multiplied by stain intensity (0 = negative, 1 = weak, 2 = moderate, 3 = strong) for each specimen. High expression of MRS was assigned scores of ≥3. Results: For the tissue sections, MRS protein showed higher positivity in PDAC (91.4%, n = 70) compared with the normal pancreatic tissues (14.6%, n = 64), indicating that MRS protein is frequently upregulated in PDAC tissue compared with normal pancreatic tissue. Overexpression of MRS was closely related with larger tumor size and positive lymph node metastasis. However, it was not correlated with patient gender, age, Lymph vascular invasion and micro-satellite instability (MSI) status. Conclusion: High expression of MRS has a shorter overall survival (OS) and disease-free survival (DFS) than those with low expression (Log Rank = 13.826 and 7.749, respectively; p = 0.000 and 0.017, respectively). Conclusion: Survival analysis showed that patients with MRS high expression level had significantly lower OS and DFS than that with MRS low expression level. Therefore, high expression of MRS is associated with poor clinical survival in PDAC. Our results demonstrated that MRS may serve as a novel biomarker for prognosis in pancreatic cancer.

Su2032
Impact of HIV Infection on Survival in Patients With Colorectal Cancer: A Systematic Review and Meta-Analysis
Sashidhar Manthravadi, Swathi Paleti, Madhusudhana Sheshadr
Background: HIV has been associated with an increased incidence of several non-AIDS defining cancers, including colorectal cancer. While HIV infection is a known prognostic factor in AIDS-defining malignancies, the impact of HIV infection on survival in colorectal cancer (CRC) is not well known. Methods: A systematic literature search from inception through to up November 2015 was performed utilizing PubMed and Embase to identify studies that described the impact of presence of HIV infection in patients with colorectal cancer. Summary adjusted hazard ratio (HR) estimates with 95% confidence intervals (CI) were estimated using a random effects model. The heterogeneity was assessed using the I^2 square test of homogeneity and the inconsistency index. Results: After searching through 1032 abstracts, 8 studies were selected and data was extracted (Table). Four of these 8 studies were reported from Europe and the 2 remaining studies were reported from the United States. The impact of HIV status on overall survival and cancer-specific survival was described in 5 and 2 studies respectively. A total of 263,553 patients with colorectal cancer were included across all 8 studies, of whom 490 also had a concomitant HIV infection. In a meta-analysis which included 263,854 patients, HIV was associated with improved overall survival (pooled HR 2.36, 95% CI 1.80-3.63) with low heterogeneity (I^2 = 27%). The association of HIV with adverse prognosis remained significant when analysis was restricted to studies which reported cancer stage-adjusted hazard ratios (by hazard ratio 1.69-4.71) We also found that HIV was associated with lower rates of cancer-specific mortality in a meta-analysis after adjustment for cancer treatment (2 studies, 263,094 patients; HR 1.41, 95% CI 1.12-1.78). Conclusions: Concurrent HIV infection appear to confer adverse prognostic in patients with colorectal cancer. However and in this is due to variation in the biologic properties of CRC in patients with HIV or due to disparities in cancer treatment. Additional studies are required to further understand this relationship.

Author Year Location CRC Stages Included HIV Status n HIV CRC non-HIV CRC Stage Adjusted Rx Adjusted HAART Adjusted
Marcus 2015 USA 14V 53 646 Yes Yes No
Coghill 2015 USA 1.4V 374 261981 Yes Yes No
Dal Maso 2014 Italy NA 6 30 No No No
Komar 2012 USA 1.4V 17 42 No No No
Somov 2010 USA NA 9 314 Yes No No
Berti 2009 Italy 1.4V 27 54 Yes No No

Abbreviations: Rx: Cancer treatment, HAART: highly active anti-retroviral therapy

Impact of HIV infection on overall survival in CRC

Su2033
Epithelial Expression of Inflammatory Caspases-4 and -5 Is Specific to Malnourig in Colorectal Cancer Patients
Brian Flood, Katarzyna Olczyska, Joanna Fay, Anthony O’Grady, Elizabeth Ryan, Glen A. Doberty, Elaine Kay, Emma M. Creagh

The inflammatory caspases are a group of proteolytic enzymes encoded by three main genes in humans: Caspase-1, Caspase-4, and Caspase-5. Inflamatory caspases are essential components of the innate immune system, as they mediate: (i) the maturation and secretion of inflammatory cytokines IL-1beta and IL-18, and (ii) pyroptosis (an inflammatory form of cell death), which limits the replication of invading pathogens and releases inflammatory cytokines and danger signals. Caspase-1 has been linked to the pathogenesis of intestinal diseases, such as inflammatory bowel disease (IBD) and colorectal cancer (CRC). We have recently implicated inflammatory caspases-4 and -5 with a role in the intestinal inflammation in ulcerative colitis (UC) patients, as expression caspase-4 and -5 in inflating immune cells within the lamina propria of UC patient biopsies correlates with their inflammation and disease activity scores. Examination of resection tissue from patients with IBD-associated CRC also revealed increased expression of caspases-4 and -5 within inflating immune cells. Strikingly, epithelial cells within areas of malignan CRC tissue expressed robust levels of caspases-4 and -5. Examination of adjacent-normal, inflamed and tumour tissue confirmed that epithelial expression is restricted to neoplastic. These observations were found in cohorts of both IBD-associated CRC and sporadic CRC patients, at stages of dysplasia and early stage (T1) CRC. Furthermore, caspase-4 expression levels were found to correlate high expression of MRS had a shorter overall survival (OS) and disease-free survival (DFS) than those with low expression (Log Rank = 13.826 and 7.749, respectively; p = 0.000 and 0.017, respectively). Conclusion: Survival analysis showed that patients with MRS high expression level had significantly lower OS and DFS than that with MRS low expression level. Therefore, high expression of MRS is associated with poor clinical survival in PDAC. Our results demonstrated that MRS may serve as a novel biomarker for prognosis in pancreatic cancer.
with increasing tumour grade. Early stage CRC is often difficult to detect pathologically, especially in inflamed tissue from IBD patients. This study identifies capses-8 and 9 as potential biomarkers for the diagnosis and staging of CRC, particularly in the context of IBD patient care.

Su2034
Identification of Potential New Biomarkers for Early Diagnosis of Gastric Adenocarcinoma: Metabolomics and Transcriptomics Analyses of Gastric Intestinal Metaplasia
Getum Andenasen, HiroyukiTomura, RuyuVetrakul,JomErkGronbech,Chun-MeiZhao,DaunChen

Background/aim: Gastric intestinal metaplasia is a breakpoint in the process towards carcinogenesis. Pathological appearances of metaplasia, dysplasia and adenocarcinoma can occur at the same time but at different sites within the same stomach. In the present study we used metabolomics and transcriptomics, we analyzed specifically the metaplasia in comparisons with cancer and non-cancer tissues in the same patients in order to identify potential new biomarkers for early diagnosis of gastric cancer. Methods: Seventeen patients with gastric adenocarcinoma (intestinal and diffuse types) underwent total subtotal gastrectomy during 2012-2014 at St. Olavs Hospital. Tissue samples were collected from 4 predetermined sites of the stomach, i.e., major and minor curvatures of body, antrum and cardia, after removal of the stomach. All the samples were reviewed according to the Japanese pathological classification. Metabolic profiling was performed using high resolution magic angle spinning NMR spectroscopy and subsequent principal component analysis (PCA). Gene expression profiling was performed using microarray (Affymetrix) and subsequent GeneChip pathway analysis. The study was approved by the Regional Committee for Medical and Health Research Ethics. Results: PCA analysis showed that there were distinct differences between metaplasia and cancerous tissues and that no differences between metaplasia and neoplasia in both metabolomics and gene expression profiles. The differences in metabolomics profile in the stage of metaplasia was mainly contributed by extremely high levels of choline (15x10^6 folds). Comparisons between metaplasia and non-cancer tissues revealed the following up-regulated metabolic pathways: GalNAcbeta1-3Gal pathway (p=2x10^-1), 1,2-diacylglycerol-3-phosphate pathway (p=1x10^-3), N-acetylglucosamine phosphate pathway (p=1x10^-2), 1,2-diacylglycerol-3-phosphate pathway (p=1x10^-3), N-acetylglucosamine phosphate pathway (p=1x10^-3), and 1-acylglucosamine-3-phosphate pathway (p=1x10^-3), histrionic-glutamate-glutamine and proline metabolism (p=1x10^-3). Most notably, the following neoplastic and disease biomarker networks were highly upregulated in metaplasia cancerous stomachs: (p=0.010, FDR=3x10^-7), immune system disease (p=2x10^-6, FDR=2x10^-7), and inflammation (p=1x10^-4, FDR=6x10^-5). In the stomach diseases, top genes and pathways included XNR2, Noxin (a stress-induced gene), NOTCH1, NOTCH2, NOTCH3, COX-2, HIWI, ionotropic glutamate receptor, and microRNA223, and Cytoskeleton remodeling_TGF, WNT and cytoskeletal remodeling (p=1x10^-7) and Development_Regulation of EMT (p=1x10^-7). Conclusion: Potential new biomarkers for early diagnosis of gastric adenocarcinoma are choline and stomach diseases biomarker network (such as XNR2, Noxin, NOTCH1 and microRNA223 and WNT signaling).

Su2035
Tumor Associated Neutrophils (TAN) in Colorectal Adenocarcinoma (CRC)
Ryan Berry, AlissaGrenenbaum, Meng-JunXiong, Katherine T Morris, Ellen J Beswick, Joshua A. Hanson

Tumor associated inflammation has been studied as a potential prognostic marker in gastro-intestinal tract cancers. Intratumoral lymphocytes have been associated with favorable prognoses in CRC. In gastric adenocarcinomas, TANs have been shown to be an independent and unfavorable prognostic factor. However, the role of TANs in determining CRC prognosis and association with morphological features that influence prognosis is not clear. To assess the prognostic significance of TANs in CRC, we retrospectively identified 248 patients (121 male, 127 female) with non-rectal (excluding cancerous treatment) treated CRC. They were treated before 2007 at our institution and had complete follow-up survival data (median of 3 years). A total of 24 patients were categorized to incomplete clinical data. CRC cases with a history of Lynch Syndrome, Familial Adenomatous Polyposis, and Inflammatory Bowel Disease were excluded from the study. Two representative slides from each case were selected for TAN counts. Ten overlapping high power fields (×400) were examined per slide (20 fields per patient). TANs were counted (avoiding areas of intact-like necrosis and ulceration) and divided into three categories based on the average number of TANs per HPF: low (0-10), medium (11-50), and high (51-200). Kaplan-Meier analysis was performed to analyze the influence TAN counts had on the median overall survival (OS). The median TAN count for all stages was 5/8 HPF. There was no significant difference in OS by low, medium, and high TAN counts for all stages (p=0.007). Stage 1 patients were as follows: Stage 1= 7/0 HPF, Stage II= 4/2 HPF, and Stage III = 3/8 HPF. Stage IV= 1/20 HPF. For each individual stage, TAN counts above or below the median for that stage showed no significant influence on OS. However, in stage II disease, statistical significance was approached with a trend toward improved survival with higher TAN counts (p=0.057, Table 1). The prognostic significance of TAN counts appears to be limited to stage II disease and suggests a trend of improved OS with higher TANs. This may prove clinically useful in stage II patients regarding the need for adjuvant treatment if the trend drifts closer towards significance in a larger sample size.

Table 1: Tumor Associated Neutrophil (TAN) Count Distribution by Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Median TAN (HPF)</th>
<th>Median OS (&lt; 10) TAN Count</th>
<th>Median OS (11-50) TAN Count</th>
<th>Median OS (51-200) TAN Count</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (29)</td>
<td>7.0</td>
<td>151</td>
<td>151</td>
<td>151</td>
<td>0.544</td>
</tr>
<tr>
<td>2 (94)</td>
<td>4.2</td>
<td>159</td>
<td>91</td>
<td>91</td>
<td>0.057</td>
</tr>
<tr>
<td>3 (91)</td>
<td>5.8</td>
<td>58</td>
<td>70</td>
<td>70</td>
<td>0.495</td>
</tr>
<tr>
<td>4 (130)</td>
<td>1.2</td>
<td>24</td>
<td>29</td>
<td>29</td>
<td>0.873</td>
</tr>
</tbody>
</table>

Su2036
Apolipoprotein D Is a Potential Urine Biomarker for Colorectal Neoplasia
Joshua A. Hanson, HassanBrim, Syed-MehdiNouraie, Adeyinka O. Laiyemo

Abstract Background and Aims: African Americans have higher colorectal cancer (CRC) incidence and mortality than Whites. Risk factors for this disparity are not well known. Robust non-invasive CRC screening tests will likely reduce this disparity, knowing that AA have the lowest adherence rate to colonoscopy that associate with advanced lesions at diagnosis. We aimed to determine potential proteomic markers in urine of patients with colorectal neoplasia. Methods: We used urine samples from 20 patients (5 normals; 6 polyps, 6 adenomas and 3 cancers). Urine dipstick test was used to choose only specimens with negative or trace protein values (≤ 0.15 mg/dL). The selected specimens were trypsin-digested and run in a mass spectrometer (MS). Proteome Discoverer v2.2 was used for qualitative analysis where SILVE was used for quantitative data analysis and Cramine was used for normalization. Ingenuity Pathway Analysis (IPA) was used to map the proteins to known pathways. Results: When comparing normal and cancer urine proteomic profiles, 391 proteins were statistically different. SILVE analysis showed 16 proteins were highly significantly different between the normal and cancer urine samples. The cancer urine samples did not contain 8 proteins which showed a decrease in levels in the cancer urine samples as compared to the normal. Conclusion: We found proteomic markers related to metabolism and immunity that have a potential to be used as a non-invasive screening of colorectal cancer patients’ urine samples. These markers need to be validated in a larger cohort.

Su2037
CD8+ T-Cell Infiltration in Epithelial and Stromal Tissues of MSI Colorectal Cancer Patients

BACKGROUND: Microsatellite instability (MSI-H) is seen in 10-15% of sporadic colorectal carcinomas (CRC) and is associated with good prognosis and a high density of tumor infiltrating lymphocytes (TILs) more than T-cells. AIM: To evaluate the association of CD8+ T-cell infiltration in colon epithelial and stromal mucosa of African American patients with MSI-H colorectal cancer. METHODS: Tissues were micro-dissected from FFPE (Fresh frozen paraffin-embedded) blocks of 34 patients in a tissue microarray (TMA). These samples contain 29 cases of MSI-H CRCs and 5 matched normals. CD8+ T-cell densities/counts both in tumor epithelium and stromal compartment were analyzed by immunohistochemistry by reading the intensity of staining and the number of stained cells by two pathologists. RESULTS: The median (IQR) for intraperthelial CD8+ T-cell was 2 (1.3-6) while the stromal lymphocytes number (SLN) was 40 (20-68). All samples had 3+ intraperthelial and stromal density for CD8+ T-cells, the percentage being higher in females (median of 3 vs. 1 in males) and higher in stage 2 (median of 1, 4 and 2 in stage 1, 2 and 3) tumors. SLN number was higher in proximal tumors (median of 50 vs. 20 in distal tumors). CONCLUSION: The MSI with CD8 profile defines a subset of CRCS with special molecular etiology and background. The ratio of the immune cells in the stromal and the epithelial compartments can help to define the MSI subtype of tumors, which will further help in targeted immunotherapy for a better outcome.

Su2038
Preoperative Thrombocytosis As a Possible Prognostic Factor for Recurrence After R0 Gastric Cancer Resection
Ana Borda, Eduardo Albenz, Juan J. Vila, Ignacio Fernandez-Urreta, Jose Manuel Zozaya, Ana Guerra

INTRODUCTION: It has been postulated that thrombocytosis could be related with a poor prognosis, with few data about its possible predictive value in tumoral relapse after a radical resection. AIM: To analysed the possible prognostic value of a preoperative elevated platelet