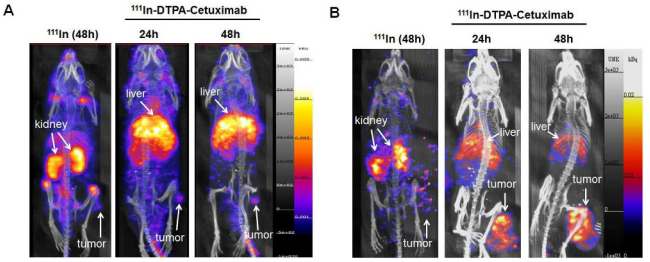

^{111}In-DTPA-Cetuximab was utilized to diagnose early and advanced colorectal cancer in HCT-15-induced xenografts. (A) The early tumors (n=3) implanted in nude mice for 1 week (50 mm^3) were detected using ^{111}In-DTPA-Cetuximab cooperated with SPECT/CT. The radioactive image in the tumor of ^{111}In-DTPA-Cetuximab group was apparently observed both in 24h and 48h, and higher than that in In-111 group. ^{111}In-DTPA-Cetuximab majorly accumulated in liver and tumor, otherwise In-111 accumulated only in kidney. (B) The advanced tumor (250 mm^3) was established and imaged. The tumors in ^{111}In-DTPA-Cetuximab group were apparently detected and imaged, and radioactive signals were higher than that in In-111 group.

Su2030

Pre-Treatment Neutrophil, Lymphocyte and Platelet Counts in Mismatch Repair Deficient Colorectal Cancer

Shahrooz Rashtak, Xiaoyang Ruan, Ruth Johnson, Brooke R. Druliner, Donna Felmlee 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 increase inflammatory infiltrates suggestive of immunogenicity 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 regarding tumor stage, leukocyte counts and differentials within 30 days prior to the 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 38.9 (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 significant. 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 one 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 neurophil 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-tRNAsynthetase Serves as a New Prognostic Marker in Pancreatic Cancer

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Background and aims: Overexpression of methionyl-tRNAsynthetase (MRS) was reported 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 2015. 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 MRS positive cells multiplied by stain intensity (0= negative, 1= weak, 2= medium, 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%, 64/ 70) compared with the normal pancreas tissues (14.6%, 6/41), 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 differentiation. In addition, The Kaplan-Meier survival curves indicated that patients with high expression of MRS had a shorter overall survival (OS) and disease-free survival (DFS) than those with low expression (Log Rank = 13.828 and 5.749, 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

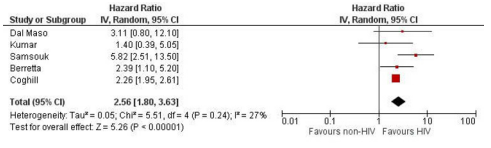
Impact of HIV Infection on Survival in Patients With Colorectal Cancer: A Systematic Review and Meta-Analysis

Sashidhar Manthravadi, Swathi Paleti, Madhusudhana Sheshadri

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 up to 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 chi square test of homogeneity and the inconsistency index. Results: After searching through 1032 abstracts, 6 studies were selected and data was extracted (Table). Four of these 6 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 6 studies, of whom 486 also had a concomitant HIV infection. In a meta-analysis which included 262,854 patients, HIV was associated with improved overall survival (pooled HR 2.56; 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 (3 studies, HR 2.82; 95% CI 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, 263,054 patients; HR 1.41; 95% CI 1.12-1.78). Conclusions: Concurrent HIV infection appear to confer adverse prognosis in patients with colorectal cancer. However, it is unclear if 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
Characteristics of included studies

Author	Year	Location	CRC Stages Included	HIV CRC	non-HIV CRC	Stage Adjusted	Rx Adjusted	HAART Adjusted
Marcus	2015	USA	I-IV	53	646	Yes	Yes	No
Coghill	2015	USA	I-IV	374	261981	Yes	Yes	No
Dal Maso	2014	Italy	NA	6	30	No	No	No
Kumar	2012	USA	I-IV	17	42	No	No	No
Somsouk	2010	USA	NA	9	314	Yes	No	No
Berretta	2009	Italy	I-IV	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 Malignancy in Colorectal Cancer Patients

Brian Flood, Katarzyna Oficjalska, Joanna Fay, Anthony O'Grady, Elizabeth Ryan, Glen A. Doherty, 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*. Inflammatory 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 of caspase-4 and -5 in infiltrating 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 infiltrating immune cells. Strikingly, epithelial cells within areas of malignant 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 tissue. 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

with increasing tumour grade. Early stage CRC is often difficult to detect pathologically, especially in inflamed tissue from IBD patients. This study identifies caspases-4 and -5 as potential biomarkers for the diagnosis and staging of CRC, particularly in the context of IBD patient surveillance.

Su2034

Identification of Potential New Biomarkers for Early Diagnosis of Gastric Adenocarcinoma: Metabolomics and Transcriptomics Analyses of Gastric Intestinal Metaplasia

Gøran Andersen, Hiroyuki Tomita, Riyas Vettukattil, Jon Erik Gronbech, Chun-Mei Zhao, Duan Chen

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 using 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 or 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 (Illumina) and subsequent GeneGo 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 non-cancer tissues and no differences between metaplasia and neoplasia in both metabolomics and gene expression profiles. The difference in metabolomics profile at the stage of metaplasia was mainly contributed by extremely high levels of choline ($15x10^5$ folds). Comparison between metaplasia and non-cancer tissues revealed the following upregulated metabolic pathways: GalNAcbeta1-3Gal pathway (p=$8.2x10^{-3}$), 1,2-didocosapentaenoyl-sn-glycerol_3-phosphate pathway (p=$1.6x10^{-2}$), N-acyl-sphingosine phosphate pathway (p=$1.6x10^{-2}$), 1,2-didocosahexaenoyl-sn-glycerol_3-phosphate pathway (p=$2.1x10^{-2}$), 1,2-dioleoyl-sn-glycerol_3-phosphate pathway (p=$7.5x10^{-2}$), and 1-acyl-glycerol_3-phosphocholine pathway (p=$8.9x10^{-2}$), histidine-glutamate-glutamine and proline metabolism (p=$1.1x10^{-2}$). Most remarkably, the following neoplastic and disease biomarker networks were highly upregulated in metaplasia: stomach diseases (p=$3.0x10^{-52}$, FDR=$3.3x10^{-49}$), immune system disease (p=$4.2x10^{-16}$, FDR=$2.6x10^{-14}$) and inflammation (p=$1.6x10^{-14}$, FDR=$6.9x10^{-13}$). In the stomach diseases, top genes and pathways included XRN2, Noxin (a stress-induced gene), NOTCH1, NOTCH2, NOTCH3, COX-2, HIWI, ionotropic glutamate receptor, and microRNA 223, and Cytoskeleton remodeling_TGF, WNT and cytoskeletal remodeling (p=$1.4x10^{-27}$) and Development_Regulation of EMT (p=$1.8x10^{-24}$). **Conclusion:** Potential new biomarkers for early diagnosis of gastric adenocarcinoma are choline and stomach diseases biomarker network (such as XRN2, Noxin, NOTCH1-3 and microRNA223 and WNT singling).

Su2035

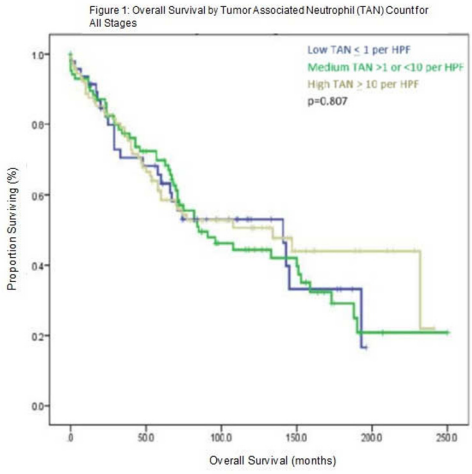
Tumor Associated Neutrophils (TAN) in Colorectal Adenocarcinoma (CRC)

Ryan Berry, Alissa Greenbaum, Meng-Jun Xiong, Katherine T Morris, Ellen J Beswick, Joshua A. Hanson

Tumor associated inflammation has been studied as a potential prognostic marker in gastrointestinal tract cancers. Intratumoral lymphocytes have been associated with a favorable prognosis in CRC. In gastric adenocarcinoma, TANs have been shown to be an independent and unfavorable prognostic factor. However, the role of TANs in determining CRC prognosis and its 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-neoadjuvant treated CRC that were resected before 2007 at our institution and had complete follow-up survival data (≥ 5 years). A total of 24 cases were excluded due 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 non-overlapping high power fields (400x) were examined per slide (20 fields per patient). TANs were counted (avoiding areas of infarct-like necrosis and ulceration) and divided into three categories based on the average number of TANs per HPF (low ≤1, medium > 1 to < 10, and high ≥10). 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=0.807, Figure 1). Median TAN counts by stage were as follows: Stage I = 7.0/HPF, Stage II = 4.2/HPF, Stage III = 5.8/HPF, Stage IV = 1.2/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

Stage (N)	Median TAN (#HPF)	Median OS (mo): TAN Count Above Stage Specific Median	Median OS (mo): TAN Count Below Stage Specific Median	P-value
1 (29)	7.0	151	151	0.544
2 (94)	4.2	159	91	0.057
3 (91)	5.8	58	70	0.493
4 (10)	1.2	24	29	0.873



Su2036

Apolipoprotein D Is a Potential Urine Biomarker for Colorectal Neoplasia

Hassan Ashktorab, Hasti Olumi, Guilherme Ventura, Namita Kumari, Songping Wang, Xionghao Lin, Sergei Nekhai, Adeyinka O. Laiyemo, Hassan Brim

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 ml/dl). The selected specimens were trypsin-digested and run in a mass spectrometry (MS). Proteome Discoverer v2.2 was used for qualitative analysis while SIEVE was used for quantitative data analysis and Creatinine 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. SIEVE analysis indicates Apolipoprotein D (Apo D) and protein kinase A anchoring protein 6 (PRKP6) as the top candidates with 65-240 and 27-138-fold induction in cancers vs. normal, respectively. However, immunoglobulin kappa constant was 7-21 folds lower in cancers when compared with normals. IPA analysis showed Apo D in the WNT pathway. C**onclusion:** We defined 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

Lakshmi Kannan, Hassan Ashktorab, Edward L. Lee, Babak Shokrani, Akbar Soleimani, Hassan Brim, Syed-Mehdi Nouraie, Adeyinka O. Laiyemo

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 (CD8+ 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 intraepithelial CD8+ T-cell was 2 (1-3%) while the stromal lymphocytes number (SLN) was 40 (20-68). All samples had 3+ intraepithelial and stromal intensity 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 characteristic clinical and pathologic features. The CD8+ T-cell infiltration within such tumors seems to be stronger in the stroma than in the tumor cells themselves. This distinction between the immune cells in the stromal and the epithelial compartments can help to profile 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 Albeniz, Juan J. Vila, Ignacio Fernandez-Urien, 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