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SO-24 Young age as bad prognosis of colorectal cancer: An earlier screening needed?

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Background: Diagnosis of colorectal cancer (CRC) at an early age has become a challenging trend for oncology worldwide, besides increased mortality in this population has emerged over the last decade. Several features of bad prognosis as an anatomic subsite, stage at diagnosis, race, and ethnicity have been studied for young adults (< 30 years old) with CRC. Nevertheless, their correlation to a bad prognosis remains unclear. This study aimed to describe the clinicopathological features and their impact on the overall survival of young Mexican adults diagnosed with CRC treated in the National Cancer Institute.

Methods: Retrospective, observational study. Included patients treated at the National Cancer Institute between 2004 and 2020. Statistical analysis required: X2 and t test, Kaplan Meier, Log Rank and Cox Regression. Statistical significance differences were assessed when p was bilaterally < 0.05.

Results: A total of 1858 patients diagnosed with CCR have attended to the National Cancer Institute. Early onset of CCR have been increasing over the last 16 years, with significant differences between the median of age, from 57 by 2004 to 55 years old by 2020 (F= 5.49; gl: 12 p= 0.019). For this analysis, population was divided in 3 groups: Young (70) 20% (n=724). Young group population was mostly man (62%; (n=63)), but the distribution was more proportionate in the other groups 50% and 53% man in the remaining groups (p=0.020). The prevalence of metastatic disease was 47% in young, 34% adults and 29% in elderly group (p=0.001). Regarding the anatomic subsite, young and adult groups had more prevalence of left-side CCR (57%), while elderly group had more frequency of right-side CCR (43%) (p=0.046). Most frequent grade observed was moderate in all groups with 46%, 55% and 58% for young, adults and elderly group respectively (p=0.750). In survival analysis, median OS was 29 months for young, versus 170 months for adults and 56 months for elderly patients' groups (p. A sub-analysis was performed taking account metastatic patients median OS was 12 months for young, versus 17 months for adults and 9 months for elderly patients' groups (p=0.008, HR 1.27, 95% CI 1.02-1.46). At Cox Regression analysis clinical stage (p=0.001; HR 1.85, 95% CI 1.75-1.96), grade (p=0.007; HR 1.29, 95% CI 1.07-1.56) and age (p=0.001; HR 1.30, 95% CI 1.08-1.87) remained as independent predictors of OS.

Conclusions: Latin American young population have demonstrated to have clinical features of bad prognosis as left-side, poor grade differentiation, and metastatic disease. The increasing young population diagnosed with CRC is a key indicator of lifestyle risk factor exposure, lack of screening and often, foreshadow tumor burden and bad prognosis of overall survival.

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SO-25 Total neoadjuvant therapy (TNT) in early-onset (EO) vs average-onset (AO) locally advanced rectal cancer (LARC): Patient characteristics and tolerance

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Background: TNT increases the rate of clinical complete response (cCR), which may allow more patients to proceed with watch-and-wait (WW) surveillance. Patients with EO (< 50 years of age) colorectal cancer (CRC) have been shown to have significantly more nausea and vomiting with adjuvant fluoropyrimidine and oxaliplatin compared to patients with AO (≥50 years) CRC. Despite the rising incidence of EO rectal cancer (RC) and increasing use of TNT, there are limited data regarding tolerance of TNT for patients with EORC.

Methods: Data from January 1, 2015 through April 28, 2021 were abstracted from our institution's IRB-approved RC database. TNT typically consisted of induction chemoradiation (50-50.4 Gy in 25-28 fractions with fluoropyrimidine) followed by tumor assessment 5 weeks later, followed by 4 months of consolidation chemotherapy (FOLFOX or CAPOX). The following characteristics were compared between EO and AO patients in this retrospective analysis: demographic features, toxicities, and treatment delivery. A Pearson's Chi-squared test and Fisher's exact test were used to compare the EO with AO patients.

Results: A total of 1,263 patients with rectal cancer were treated during the study period. Of these, 118 with LARC (clinical stage II or III) received TNT at our institution and are included in this study. There were 39 EO patients and 79 AO patients. The mean age of the EO patients and AO patients was 43 years and 62 years, respectively. Females comprised 51% of the EO patients and 33% of the AO patients (p=0.054). There were no racial or ethnic differences between the EO and AO patients. Of the 92 cancers tested for mismatch repair, only 3 were deficient (3%). Among the EO patients, 15% had an identified germline pathogenic variant. Between the EO and AO patients, there was no difference in the distribution of clinical T, N, and overall stage. There was no difference in concurrent chemotherapy or consolidation chemotherapy regimens. EO patients experienced more nausea of any grade (51% vs 29%, p =0.019) than AO patients. There was no difference in other toxicities. Dose reduction for toxicity occurred in 41% of EO patients and 61% of AO patients (p = 0.043).

Conclusions: Our retrospective analysis of TNT tolerance suggests that younger patients have higher rates of nausea but are less likely to require a dose reduction. These findings are consistent with adjuvant chemotherapy outcomes in EOCRC. Further data will be presented on the timing of nausea in order to optimize treatment for patients with EORC.

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SO-26 Identification and quantification of the microbiome in colorectal cancer metastases

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Background: Recent research has identified the existence of living bacteria in the tumor microenvironment, as well as cancer-specific bacteria in blood of patients. Early evidence suggested a role of the gut and tissue microbiome in the development of colorectal cancer (CRC). However, the part of this intra-tumor microbiome in promoting or aiding metastasis to distant organs remains unexplored. Interestingly, similar bacterial strains from CRC primary tumors have been identified in patient-matched liver metastases. Few mechanistic hypotheses have been proposed of how bacterial translocation to distant sites occurs, or whether the tumor-resident microbiome can influence the spreading or the behavior of metastases and their local immune response.

Methods: We aimed to characterize the intra-tumor bacterial signature of metastatic colorectal cancer (mCRC) through a large-scale study with different cohorts from several biobanks in Belgium. We collected 378 frozen samples from 99 patients composed by 104 primary colorectal tumors (PT) and 99 patient-matched liver metastases (LMT), both associated with normal adjacent tissue (NAT) as control (n = 83 and 58, respectively). We added primary liver tumors (hepatocellular carcinoma (HCC, n=28) and cholangiocarcinoma (CGC, n=6)) from 27 patients as comparative cohort for LMT. The V4 region of the bacterial 16S rRNA gene was sequenced. The computational DADA2 pipeline was used to process the sequencing data and determine the abundance of amplicon sequence variants (ASV). We strictly applied sterile conditions from sample collection to sequencing, with negative and positive controls along the process to minimize contamination and misinterpretation of the results. Potential contaminants were removed bioinformatically by applying a series of stringent filters.

Results: Bacterial sequences were identified in all tissue types. Based on preliminary results, the principal component analysis based on bacterial composition of the samples revealed significant sample grouping (PERMANOVA, p-value = 1e-04) per tissue type (PT, LMT and HCC-CGC). The read number and bacterial composition of associated NAT were similar to their associated tumor tissue. PT, as expected by their colonic origin, presented higher bacterial biomass than LMT, yet the patient-specific microbiome composition in LMT was partially overlapping with PT, consisting with previously reported prevalent taxa. The number of shared ASVs between PT and LMT was significantly higher within than between patients (linear regression model with p-value = 4,22e-10), suggesting an individual bacterial transfer. This transfer appeared

to be a probabilistic event, as it correlated with taxa abundance, and this transfer was more likely for the most abundant bacteria in the PT.

Conclusions: Our preliminary results suggest the presence of a low bacterial biomass in LMT with characteristics closer to PT compared to primary tumors of the liver, suggesting a "per-tumor type" rather than "per-organ" bacterial signature and abundance. A within-patient bacterial transfer from PT to LMT seems to be observed for the most abundant taxa. These preliminary results are currently in a validation process. If our results are confirmed, this multicentric large-scale study would allow us to characterize and classify tumor tissue bacterial signature in mCRC to compare it with genomic and immune tumor features.

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SO-27 Microbiome signature, global methylation and immune landscape in early onset colorectal cancer

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Background: The incidence of colorectal cancer (CRC) in young adults (age of diagnosis $<$ 50 years old) has been rapidly increasing. Approximately 20% of early-onset (EO) CRC cases are due to germline gene mutations. However, the etiology of sporadic EO CRC remains poorly understood. Research suggests that environmental factors such as Western diet may be associated with increased incidence of sporadic EO CRC. The gut microbiota decompose and ferment dietary fibers to produce microbial metabolites including vitamins such as folate. Folate is essential for one-carbon transfer and methylation metabolism through the synthesis of S-adenosyl methionine (SAM), which may influence the host epigenome. In addition, microbial metabolites regulate both innate and adaptive immune response, including dendritic cells, macrophages, CD4+ memory T cells and T regulatory (Treg) cells. Studies showed dysbiosis may promote an immunosuppressive tumor microenvironment (TME) and suppresses antitumor immune surveillance.

Methods: The aim of our work is to associate intratumoral microbiota with methylation pattern and tumor infiltrating lymphocytes (TILs) in EO CRC. A total of 358 CRC cases, including 54 cases of EO CRC and 304 cases of late onset (LO) CRC (age of diagnosis $\geq$ 50 years old), with matched methylation array (Infinium HM450), RNA-sequencing (RNA-seq) from colon adenocarcinomas (COAD) and rectal adenocarcinomas (READ), and clinicopathological information of each patient, were extracted from the Cancer Genome Atlas (TCGA). We characterized and compared the methylation profile, intra-tumor microbiota composition and TILs between EO and LO CRC.

Results: We found that there are distinct patterns of methylation, microbial, gene expression in the EO CRC when compared with LO CRC. The EO CRC cases showed global hypomethylation, and methylation ages predicted by different epigenetic clock models were older than their chronological ages in patients with EO CRC. Microbes from several kingdoms including bacteria, fungi and viruses were enriched in EO CRC. Pathway overrepresentation analysis of differentially expressed genes showed upregulation of RAS pathway, activation of inflammatory response and fatty acid metabolism. Integration across datasets showed strong correlations between specific microbes and upregulation of regulatory T cells (Tregs) and downregulation of CD4 memory T cells.

Conclusions: These data suggest that there may be accelerated aging in EO CRC, in addition, colorectal cancer-associated microbiota may be associated with epigenetic regulation and host immune response.

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SO-28 Gut microbiome characterization and correlation with colonoscopy findings in oncological and non-oncological patients from a Chilean cancer center

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Background: In 2020, more than 6,200 patients were diagnosed of colorectal cancer (CRC) in Chile, representing 11.5% of new total cancer cases that year. According to experimental evidence, the gut microbiome is involved in CRC formation, progression and its response to treatment. NGS 16S metagenomics analysis has been shown to be a useful tool for characterizing and segregating population based on gut microbiome and correlating bacterial populations with outcomes under specific clinical conditions, such as gastrointestinal cancer.

Methods: A total of 32 cases, men and women, 18-80 years old, who underwent colonoscopy were included and enrolled. All participants signed a consent letter. Fresh stools were collected for DNA extraction and sequencing using Ion 16S™ Metagenomics Kit (Thermo Fisher) and Ion GeneStudio S5. A compositional analysis was performed based on differential expression and multiple test correction, as well as alpha- and beta-biodiversity between oncological and non-oncological patients. Finally, the microbial composition and the presence of a specific microorganism was correlated with the histological findings after colonoscopy.

Results: Most of the patients with gastrointestinal lesions showed a significant modification of their gut microbiome compared to participants without pathological findings during colonoscopy, confirmed by a significant different Shannon's index per group (p-value Parvimonas and Peptostreptococcus, and reduced levels of Eubacterium, Roseburia, Bacteroides and Faecalibacterium (adjusted p-value 1). The analysis at the level of species confirmed that CRC cases had an increased prevalence of Peptostreptococcus stomatis, Parvimonas micra and Fusobacterium nucleatum (adjusted p-value $\leq$0.1 and LFC $>$1) compared with individuals diagnosed with a non-malignant lesion after colonoscopy biopsy. In addition, the association of F. nucleatum with gastrointentinal cancer was confirmed in patients recently diagnosed or after surgery (R0) (p-value $<$ 0.01).

Conclusions: Substantial changes in the abundance and occurrence of specific bacterial populations can be detected in Chilean patients with CRC, with a strong correlation with F. nucleatum and P. micra, both of which have been previously reported as potential biomarkers and outcome predictors. This is the first study performed in a local population with and without a confirmed neoplastic lesion, and allows us to build the first Chilean microbiome profile associated with a healthy and oncological gut.

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