May 9, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (ESPS Manuscript No2153-Review)

Title: Colorectal cancer in patients under 50 years of age: A retrospective analysis of two institutions' experience

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 2153

We would like to thank the reviewers for taking the time to review our manuscript regarding patients under 50 years of age with colorectal cancer. We appreciate their comments and criticisms. I will address all of their comments and questions. Let me say at the outset that the purpose of this paper is to alert doctors to the fact that the percentage of patients under age 50 with colorectal cancer is higher than previously reported. Further, it appears that, not uncommonly, there is a delay in establishing the diagnosis in younger patients as evidenced to by the significantly greater percentage of young patients with Stage 3 and 4 disease (as per the TNM Staging system as defined by the American Joint Committee on Cancer) when compared to the over 50 colorectal cancer population.

In America, at least, many internists and surgeons wrongly believe that colorectal cancer in patients under 50 years of age is uncommon and mostly found in patients with a first-degree family history of colon cancer. Because of this misconception colonoscopy is often not recommended for patients under 50 who do not have a family history of colorectal cancer. The authors hope that, after reading this article, doctors will recommend timely and complete colon evaluations for patients under 50 who present with rectal bleeding.

The manuscript has been improved according to the suggestions of reviewers:

1. Title change: Colorectal Cancer in Patients Under 50 Years of Age: A Retrospective Analysis of Two Institutions' Experience

2. References added to clarify tumor staging according to TNM Staging System by the American Joint Committee on Cancer

3. Revisions have been made according to the specific suggestions by the reviewers to the best of our ability.

Reviewer 00504161: Unfortunately, we are not able to perform genetic or protein analysis of the tumors because for the majority of the patients tumor had not been banked. Thus, fresh frozen tumor samples are not available. We also do not have access to the majority of the paraffin embedded tissue blocks because the senior author (who coordinated this study) does not have access any longer to the New York Presbyterian Hospital (Columbia campus) pathology department because he has left that institution and is now working at a different hospital (St. Luke's Roosevelt Hospital). Unfortunately, we also no longer have access to the hospital records and operative reports of the patients from New York Presbyterian Hospital.

Reviewer 00503512: Thank you for your comments. As per your suggestion, we have gone back and reviewed the data regarding tumor location in the younger (age less than 50) and older (age greater than 50) age Stage 3 and 4 patients (advanced disease). There was no significant difference in the distribution (location in the large bowel) of the tumors between the old and young patients. We also looked at tumor location in the Stage 3 and 4 young patients vs. the Stage 1 and 2 young patients and again found no significant differences in the distribution of tumors between the early and late stage patients.

Reviewer 00031835: Thank you for your comments and suggestions. As per your recommendation we have changed the title (New Title: "Colorectal cancer in patients under 50 years of age; a retrospective analysis of two institutions experience."). We have also altered the abstract (Page 2) in regards to exchanging the word "incidence" for the phrase "epidemiological characteristics." We have also dropped the word "cohort" from the Methods section as suggested.

Reviewer 00860822: Thank you for your comments and suggestions. As per your first comment we have dropped the word "cohort". We have also changed the title of the paper to: "Colorectal cancer in patients under 50 years of age; a retrospective analysis of 2 institutions experience." We hope you will find this title suitable.

Regarding your second comment regarding the fact that the time period assessed at each institution was different. The period of time studied at New York Presbyterian Hospital (2006-2009) coincides with the dates that the senior author was on staff at that institution. The senior author moved in 2009 to a different institution, St. Luke's Roosevelt Hospital where he continues to practice. The data for each time period includes all of the patients that presented to the colorectal service during that time frame. The authors are not aware of any changes in the referral pattern of patients at either institution during the two time frames. Certainly, in this time period

the adjuvant chemotherapy protocols have changed; however, this should not impact the presentation of the patients or the initial surgical care of the patients.

Regarding the reviewers 3rd comment regarding the TNM staging system (T = Tumor stage/depth, N = lymph node stage, and M = metastases) that is used in this manuscript: In the US this system, formulated by the Joint Committee on Cancer, is used for all solid tumors. Please refer to the attached TNM staging diagram included in this document. The following references provide much more detailed information regarding this staging system:

1) Sobin LH, Gospodarowicz MK, Wittekind CH, Eds. TNM Classification of Malignant Tumors, 7th ed. Wiley-Blackwell, Oxford 2009: 100-109. ISBN 978-1-4443-3241-4.
2) Edge S, Byrd D, Compton C, Fritz A, Greene Frederick, Trotti A, Eds. AJCC Cancer Staging Manual. Springer, 7th, 2009. ISBN 978-0387884400.
3) Corman M, Ed. Colon and Rectal Surgery, 5th ed. Lippincott Williams & Wilkins, 2004. 1408 pages, ISBN 978-0781740432.

Regarding the 4th comment about the abbreviation "BRBPR" (bright red blood per rectum), we have deleted this abbreviation and instead put in "rectal bleeding."

Regarding comment #5 about our lack of mortality data for the patients enrolled in 2012: This paper did not attempt to collect the intermediate or long-term survival data for the patients in the series. The only mortality data we have regards the 30 day mortality of the under 50 patients.

TABLE 22-5 Tumor Staging with Tumor-Node-Metastasis (TNM) System

Stage	*Description*
T_X	Primary tumor cannot be assessed
T_0	No evidence of primary tumor
T_{is}	Carcinoma-*in-situ*
T_1	Tumor invades submucosa
T_2	Tumor invades muscularis propria
T_3	Tumor invades through muscularis propria into the subserosa or into the nonperitonealized pericolic or perirectal tissue
T_4	Tumor directly invades other organs or structures and/or perforates the visceral peritoneum
N_X	Regional lymph nodes cannot be evaluated
N_0	No invasion of regional lymph nodes
N_1	Invasion of one to three lymph nodes
N_2	Invasion of four or more regional lymph nodes
M_X	Distant metastases cannot be determined
M_0	No distant metastases or residual tumor
M_1	Distant metastases or residual tumor present

TNM Stage	Characteristics
0	T_{is}, N_0, M_0
I	T_1, N_0, M_0 T_2, N_0, M_0
II	T_3, N_0, M_0 T_4, N_0, M_0
III	Any T, N_1, M_0 Any T, N_2, M_0
IV	Any T, Any N, M_1

Adapted from Corman M, Ed. Colon and Rectal Surgery, 5th ed. Lippincott Williams & Wilkins, 2004. 1408 pages, ISBN 978-0781740432

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*

Sincerely,

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