World Journal of Gastroenterology Manuscript No. 35495

Response to Reviewers' Comments

Reviewer #1

1. *Abstract/Results/Figure 1: I find quite misleading referring to a cohort of 14663 subjects. In fact, the paper refers to patients who had a diagnosis of AA/TSA/ASSA not associated with CRC, and with at least one surveillance colonoscopy. Only 4610 patients satisfied these criteria and this is the number of cases that was actually studied. All the others do not add any information to the study.*
   Response: We have made the change to the abstract as results only those patients with high risk polyps in which surveillance colonoscopy was completed. We include in the results section of the body of the manuscript and in Figure 1 the total of 14663 high risk polyp patients from which our study cohort was identified in order to indicate that AA/TSA/ASSA cancer found at incident colonoscopy were not confounding the rates of high risk polyp related cancer found at surveillance colonoscopy.

2. *Abstract. Please add the mean duration of follow up and inclusion criteria for patients.*
   Response: We have included the mean duration of follow up and inclusion criteria in the abstract.

3. *Abstract: please specify in the methods that the risk factors for iCRC were calculated on a sample of cases and controls, and report the corresponding numbers.*
   Response: This information has been added to the abstract.

4. *Core tip: You state that "However, screening colonoscopy has a 3.5% false negative rate for detection of CRC, resulting in 17% of patients who had undergone colon screening within 3 years being diagnosed with CRC". These figures do not appear in the main text of the paper; please report them e.g. in the introduction, with the corresponding references.*
   Response: This information has been added to paragraph 1, sentence 3 of the Introduction.

5. *Introduction: please add a reference to the very first sentence.*
   Response: This reference has been added.

6. *Introduction/discussion: You state that "In the US, surveillance is recommended 3 years after removal of AA, TSA, or advanced SSA". In fact, this applies to the US (please specify), but in other parts of the world different recommendations have been produced. For instance see the European guidelines for quality assurance in colorectal cancer screening and diagnosis (http://www.kolorektum.cz/res/file/guidelines/CRC-screening-guidelines-EC-2011-02-03.pdf), that introduced the category of intermediate risk adenomas and recommended a 1-year interval after removal of high-risk adenomas and a 3-year interval for intermediate-*

risk adenomas. Discussing the possible impact of the EU guidelines on your findings would be valuable for European readers.
Response: We have added the findings for HR for intermediate risk polyps based on polyp size in Tables 1 and 3, and address this in the results and discussion section of the manuscript.

7. *Introduction. The last paragraph could be improved by clearly declaring the aims of the study. Moreover, I did not fully understand the usefulness of the last sentence. Did I miss something?*
Response: We have rewritten this last sentence for clarity and have explained the aims of the study as well.

8. *Methods: definition of ASSA: please define the "higher number" of synchronous polyps.*
Response: We defined the "higher number" of synchronous polyps as you requested.

9. *Results, first paragraph. You found that CRC was diagnosed in 1.67% TSA/ASSA patients and in 3.14% AA patients. Please state if this difference is statistically significant.*
Response: The p-value is 0.11 and is included in the text.

Throughout the whole paper, AA, TSA and ASSA are considered together. However, it would be highly informative to report whether you observed any differences among the two/three categories of patients.
Response: We do report that there is a difference in the post polypectomy CRC rates for TSA/ASSA and AA patients as noted in the sentence highlighted in this critique.

10. *Results, second paragraph. In the text you report a series of percentages that are difficult to understand. For instance, the reader has to look at table 1 in order to understand that 47.6% vs 33.7% refer to the proportion of subjects older than 70 years. Instead, the text should be self-explicative.*
Response: We simplified this per your request by deleting these percentages from the text.

11. *Results, Figure 2b. The x-axis (years of follow up time) stops at 10 years, while in the text you refer to a median survival up to 15.2 years. I suggest to increase the x-axis of the Figure up to at least 16 years.*
Response: Thank you for the comment. Given the cohort we feel that a 10 year interval of data is very reasonable to present

12. *You included in the study patients with the index colonoscopy performed between 1990 and 2010. During this long period substantial changes in technology, procedures, knowledge about the different types of lesions took place, as well as - reasonably - in the knowhow and technical ability of endoscopists. Therefore it would be not surprising to find a significant*

temporal trend in the development of CRC during surveillance. I suggest to introduce the time-axis in your analysis.
Response: We agree with the reviewer that modelling the changes over this time period as a time-dependent covariate would be appealing; unfortunately we do not have an adequate way to account for the changes in technology and procedures. The case-cohort design allows for balance over the course of the study and should adequately balance the groups.

13. *Discussion, last paragraph. I agree with you that "this is the first study to determine risk factors for incident CRC at the same site or at another site in the colon following polypectomy of advanced lesions.". However there are studies about similar populations, that could be cited. See for instance, Atkin W et al. Lancet Oncol. 2017 Jun;18(6):823-834.*
Response: We cited the Atkin et al study as you requested.

14. *Table 1. Time interval… = 4.24, which is different from the 2.31 in text. The same difference applies to Table 3. Did I miss something?*
Response: We are reporting 2 intervals in the text. The first interval (4.24) is the time from first colonoscopy (when the high risk polyp was resected) to cancer. The second interval (2.31) is the time from last colonoscopy (which was done after polypectomy for surveillance) to cancer.

15. *Table 1 and table 3. Asterisks for statistically significant p-values are not necessary.*
Response: These asterisks have been removed.

16. *Table 1 and table 3. Please specify that p-values are referred to univariate analysis.*
Response: The p-values actual are comparing between the groups and are not model based. We have added the methods of calculation as a footnote.

Reviewer 2

1. *In the section of statistical analysis, why the authors included only cancer occurring at one year after the ultimate polypectomy? But in the section of results, the authors calculated the median time from the index polypectomy to interval cancer development was 3.5 years for patients who developed CRC after the index polypectomy was not seen on the next surveillance. The data seemed to be conflicted.*
Response: We included only cancers that arose at least one year after the index polypectomy. We have corrected that in the body of the manuscript.

2. *The authors tried to find the risk factors for the CRC following index polypectomy. The control group patients (with index polypectomy and not later develop CRC) were "randomly"*

selected. The method how to random selection of control group and the rationale of the method use should be explained
Response: We have explained the random selection of this control group in the Methods section, first full paragraph on page 8, sentences 5.

3. *In the section of results, the causes associated with CRC development in patients who developed interval CRC at the section site included non-adherence to the recommended surveillance interval (27.4%), incomplete resection of high risk polyp (25%) and unknown causes (30%). The causes associated with interval cancer development at another site were non-adherence to recommended surveillance interval (31.5%), unknown cause (27.8%) and incomplete colonoscopy (36.0). As we know, interval cancer is defined as "colorectal cancer diagnosed after a screening or surveillance exam in which no cancer is detected, and before the date of the next recommended exam" (Sanduleanu S, et al. Gut 2015;64:1257–1267). Therefore, the CRC developed due to non-adherence to the recommended surveillance cannot be called as interval cancer*
Response: We agree with the reviewer and have made the appropriate changes. Our goal is to study risk factors associated with cancer development after polypectomy (not interval CRC). We removed the word "interval "from the manuscript.

Reviewer 3

1. *This study deals with an innovative, well-speculated clinical question. The manuscript has been well conducted and the paper has been clearly written and is interesting. However, there are minor concerns: - The title is too risky and not supported by the conclusions of the study.*
Response: We appreciate your comments but we support the title since these patients developed cancer despite knowing that they were at high risk and despite receiving surveillance colonoscopy.

2. *In the abstract, the introduction is long and methods are not explained at all. - There is no consensus on the definition of interval CCR*
Response: We have made some clarifications in the methods as you requested. We removed the word" interval" from the manuscript as we mentioned above.

3. *The authors should explain the concept of "interval CCR" in methods. - They use the same abbreviation (EMR) for two meanings.*
Response: We deleted the abbreviation (EMR) for electronic medical record. We thank you for the valid comment.

Reviewer 4

1. *This paper reports the incidence of colorectal cancer in a cohort of subjects under colonoscopy surveillance after advanced/serrated adenoma resection. Data are interesting and the paper is well written. Major comments: None Minor comments: Abstract: the methods section of the abstract should be rewritten in order to better describe patients' selection.*
   Response: We appreciate your comment. The section was rewritten.

2. *Page 6, paragraph 2. This phrase should be removed here as it describes results: "From this group 4160 patients had at least one surveillance exam following the index polypectomy for their AA/TSA/ASSA.*
   Response: We appreciate your comment. We will keep in the method section we would like to give an idea about the patients we included and the type of polyps which were resected before getting to the results section.

3. *Page 6, paragraph 3. Figure 1 should be cited in the first paragraph of the results section of the paper as it describes results and not methods.*
   Response: We agree with the reviewer and we moved it to the results sections.

4. *Page 8, paragraph 2. Demographic (age, sex) characteristics of the 4610 patients with surveillance colonoscopy should be reported here as well as the number and time interval of surveillance colonoscopies (e.g. using mean, median or quartiles…).*
   Response: This information was collected and is indirectly reported in Tables 1 and 3 but with regard just to the selected cohort.

5. *Page 8, paragraph 3. "These 84 patients were compared to a randomly selected cohort of 252 of the AA/TSA/ASSA patients who did not develop interval CRC." Authors should better explain in the methods section why they compared these 84 patients to a randomly selected cohort and not to the entire cohort the AA/TSA/ASSA patients who did not develop interval CRC.*
   Response: This is addressed now in expanded section regarding the random selection of this control group in the Methods section, first full paragraph on page 8.

6. *The same comment applies to the last paragraph of page 9. Figure 1: A box with the total number of patients with AA/TSA/ASSA should be placed at the top of the flow chart.*
   Response: We appreciate your comment. We felt that the flow chart is very busy and adding more data to it will make it difficult to interpret. We reported this information in the results section.

Reviewer 5

1. *An interesting paper, in a nice, well-described cohort, analysis is solid. One may come to a different conclusion though that current guidelines are strong enough. The interval cancer of 1.8% at the same location as the polyp is for sure less than the possible missed polyp rate even when colonoscopy is performed in a well-prepped patient with good standards. So, I believe that data should be interpreted as, interval cancer rate is low but not zero. Therefore please modify discussion and conclusion*
   Response: We agree with the invaluable comment. We feel that 3% is a high number when expected to be 0% or close to 0%. Agree that the current guidelines are strong enough but still limited.

2. *Moreover cancers at other location are for sure nothing else than missed polyp, which reflect reality.*
   Response: We agree and one major point of this manuscript is the importance of doing a thorough colonoscopy at surveillance for an AA/TSA/ASSA that includes inspection of the entire colon at every surveillance exam, being aware not to focus just at the site of the known AA/TSA/ASSA.

3. *Another comment is if authors have noted any time trends and association with year of initial colonoscopy?*
   Response: This is an interesting recommendation but beyond the scope of the paper.