April 10, 2022

Dear Dr. Ahmed, Dr. Burada the *World Journal of Gastrointestinal Oncology* Editorial Board,

Attached please find our revised manuscript submission to *WJGO* entitled "Contemporary, National Patterns of Surgery after Preoperative Therapy for Stage II/III Rectal Adenocarcinoma (Manuscript NO.: 74557, Retrospective Cohort Study)." The manuscript has been improved according to the suggestions of reviewers (all changes have been highlighted the text):

Reviewer 1
The outcome indicators were too complex and the discussion did not highlight the key points. It is suggested that the author focus on the analysis of the main indicators in the discussion part. Simutaneously, please compare it with the literature, and analyze the reasons for this phenomenon so as to get the final conclusion.

Response: Thank you for your review. We have tried to clarify that our primary outcome was rate of sphincter sparing surgery, and secondary outcome were proportion of cases approached using open, laparoscopic or robotic approaches, surgical quality as defined by resection margin and lymph node harvest, and overall survival (Methods of Abstract, p2; and "Outcomes/Definitions" portion of Methods section as below, p4-5):

(p2) Methods: A retrospective cohort was created using the National Cancer Database. Primary outcome was rate of sphincter-sparing surgery after neoadjuvant therapy. Secondary outcomes were surgical approach (open, laparoscopic, or robotic), surgical quality (R0 resection and 12+ lymph nodes), and overall survival.

(p4-5) Outcomes/Definitions
To describe patterns of surgical care delivery, the primary outcome was proportion of patients receiving local excision or TME with or without sphincter preservation.
…
Surgical approach to TME was subcategorized into open, laparoscopic, and robotic.
…
Secondary outcomes that were assessed include pathologic stage, quality of surgical resection, and overall survival.

Response: In addition, we have tried to maintain a focused discussion summarizing the findings of the study as they related to the primary and secondary outcomes in the first paragraph of the discussion (p8), comparing the primary outcome of sphincter preservation to literature and noting important study limitations (p9), providing context and interpretation of the secondary outcome of MIS approaches and improved survival found in this study that is at odds with prior studies (p9-10):

(p8)
Neoadjuvant treatment at the population level does not seem to affect sphincter-sparing rates. Interestingly, this cohort also showed improved survival in cases approached minimally invasively - a finding that is at odds with prior, high-quality randomized control trials, but may reflect important differences between the randomized control trial population and surgeon and patient selection that occurs in broader practice.

(p9)
A majority of patients in our cohort underwent some type of neoadjuvant treatment, and sphincter-sparing rates were similar in patients with stage II or stage III disease. Prior meta-analysis supports the approximate rate of permanent colostomy to be approximately 30%.[21] It is important to note that

certain clinical features, such as tumor distance from the anal verge or patients' prior continence status, which might influence the decision for a non-sphincter sparing operation, are not available in this dataset.

(P9-10)
However, adoption of MIS for rectal cancer has been controversial, as both the Z6051 and ALaCaRT trials were unable to establish non-inferiority of pathological outcomes for minimally invasive vs open resection in patients with rectal cancer.[25,26] Follow-up of these trials found no significant difference in survival between approaches, with Z6051 showing 2-year disease free survival (DFS) of 79.5% in the laparoscopic group and 83.5% in the open group and ALaCaRT showing 2-year DFS of 94% in the laparoscopic group and 93% in the open group.[27,28] Finally, the ROLARR trial found no significant difference in conversion to open laparotomy between conventional laparoscopy vs robotic-assisted surgery, and concluded no short term benefit of robotic surgery over laparoscopy.[29] Our findings of improved survival with minimally invasive approaches, even after adjustment for pathological stage, neoadjuvant treatment, and patient/center features, are at odds with these prior, high-quality studies.

Reviewer 2
In this study, the authors wanted to show the trend of changes in surgery, but the evidence is too weak. Regarding overall survival, the authors have shown that minimally invasive surgery has a better overall survival rate compared with open surgery. If so, it can be seen that the wrong procedure was chosen when open surgery was performed in more than 2/3 of cases in 2010..

Response: Thank you for your review. Increasing MIS surgery for rectal cancer was not an 'a priori' hypothesis of this study, as the broad option of laparoscopy and robotics have been previously studied and described. However, we did evaluate surgical approach in the context of sphincter preservation, surgical quality, and survival. Therefore, it was notable from an analytic standpoint that over the years study, as the reviewer point out, surgeons gradually shifted from using open approach 2/3 of the time in 2010 to MIS 2/3 of the time in 2016 (**Figure 2**). However, because this is a retrospective study, and there is inherent selection bias that we may not be able to determine (e.g. maybe in 2010 surgeons at a particular site didn't have access or skillset to use robotic platform?) we were explicit not to make conclusions about a 'right' or 'wrong' approach (p10:

For example, it is unclear if the improved resection margins and lymph node harvest in the laparoscopic and robotic subgroups are due to the approaches themselves or the cases that lent themselves to be approached minimally invasively (or the surgeons choosing a minimally invasive approach in these cases). Additionally, our findings are limited by the absence of information regarding local recurrence rate. However, it is notable that this effect of surgical approach on survival in this national cohort was maintained even after adjustment for multiple confounders or when stratifying the analysis by the subgroups with and without sphincter preservation.

Reviewer 3
Both the merits and demerits of the article are outstanding. This article aims to explore the clinical outcome of different diagnosis and treatment modes of locally advanced rectal cancer, which is novel and closely related to the clinic. And the sample size of the article is very large. The disadvantage is that the content is too complicated, the author's content and discussion results are not discussed around the main outcome index, the explanation of the results is not clear, the outcome of the article and the main line of discussion are not clear. Authors need to establish their own main outcome index, and according to this index to conduct data analysis and results discussion.

Response: Thank you for your review. As with Reviewer 1's comments, we have tried to make explicit our primary primary outcome was rate of sphincter sparing surgery, and secondary outcomes were proportion of cases approached using open, laparoscopic or robotic approaches, surgical quality as defined by resection margin and lymph node harvest, and overall survival (Methods of Abstract, p2; and "Outcomes/Definitions" portion of Methods section as below, p4-5). We have organized the results by discussing sphincter preservation in the context of stage and treatment, followed by focused results on surgical approach, surgical quality, and overall survival (p6-8). Finally, we have tried to maintain a focused discussion summarizing the findings of the study as they related to the primary and secondary outcomes in the first paragraph of the discussion (p8), comparing the primary outcome of sphincter preservation to literature and noting important study limitations (p9), providing context and interpretation of the secondary outcome of MIS approaches and improved survival found in this study that is at odds with prior studies (p9-10). These changes highlighted as part of response to Reviewer 1.

We have tried to ensure the conclusion addresses the outcomes in this study, focusing on associations that were found (p11):
At a national level, minimally invasive surgery has become the predominant approach for rectal cancer. Sphincter preservation rates, when patients undergo surgical resection, do not vary with delivery of neoadjuvant treatment. In this broad national cohort, both open surgery and non-sphincter sparing operations were associated with worse overall survival for patients with stage II/III rectal adenocarcinoma.

Science Editor
This manuscript explored the clinical efficacy of diagnostic and treatment modalities for stage II/III rectal adenocarcinoma. The content of this manuscript is overly complex, the content and discussion results are not discussed around the main result index, the interpretation of the results is not clear, and the main line of the results and discussion in the article is not clear.

Response: Thank you for your review. See above our responses to Reviewer 1-3, as well as the highlighted changes as we organize the study methods, results, discussion and conclusion based on explicit primary and secondary outcomes. We hope the above changes also address your concerns for clarification. No additional changes made based this review.

Company editor-in-chief
1. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.
2. (2) Requirements for Tables: Please provide decomposable Tables (in which all components are movable and editable), organize them into a single Word file, and submit as "74557-Tables.docx" on the system. The tables should be uploaded to the file destination of "Table File".

Response: Tables have been reorganized into one file, labelled *74557-Tables.docx.* Also included is *74557-Tables.xlsx*. The word file does not allow 'hiding' and 'unhiding' of the files as suggested, so the full tables are included in the word document. The excel file that has files hidden, and can be unhidden as reviewers request. We have left Table titles and 'three-line tables' as requested, in revised manuscript file for sake of completion/tracking (p17).

3. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022
4. Requirements for Figures: Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file, and submit as "74557-Figures.pptx" on the system. The figures should be uploaded to the file destination of "Image File". Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

Response: All figures are original. Figures have been reorganized into one file, labeled *74557-Figures.pptx,* to include copyright label as requested. Figure captions are included in revised manuscript file for sake of completion/tracking (p16).

Response: The following renamed files are all included in revision submission:

(1) 74557- Answering Reviewers
(2) 74557- Revised Manuscript
(3) 74557- Biostatistics Review Certificate
(4) 74557-Conflict-of-Interest Disclosure Form
(5) 74557-Copyright License Agreement – please note this is e-signed by all authors as of 04.10.2022. If you'd like print copies once accepted I will circulate form once more for approval.
(6) 74557-Institutional Review Board Approval Form or Document
(7) 74557-Figures
(8,9) 74557-Table Files (.docx, .xlsx)
(10) 74557-STROBE Statement
(11) 74557-Appendix A

We are thankful for the opportunity to submit this revised work and are appreciative of our reviewers' time and energy directed at reviewing this work.

Thank you for your consideration.

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Vlad V. Simianu, MD MPH
Medical Director, Colorectal Cancer Service Line, Virginia Mason Cancer Institute
Department of Surgery, Virginia Mason Medical Center
1100 Ninth Ave, C6-GS
Seattle, WA 98101
Phone 206-341-0060
Fax: 206-625-7245
Email: Val.Simianu@virginiamason.org
Twitter: @ValSimianu