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World Journal of Gastrointestinal Oncology

Title: Outcomes of neoadjuvant chemoradiotherapy followed by radical resection for
T4 colorectal cancer

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Wei-Chih Su, Tsung-Kun Chang, Ming-Yii Huang, Jaw-Yuan Wang

Dear Editor-in-Chief:

Editorial Board Member of World Journal of Gastrointestinal Oncology:

Enclosed please find my revised manuscript together with my detailed response to the referee's comments. I have read and agree to submit the revised version of our manuscript. We have made several corrections and response as reviewers' comments in the following response letter. The changes in the manuscript are highlighted with **red color (Please refer to uploaded revised manuscript with marked changes in the Supplementary Material file)**. Several references have also been added to the revised manuscript accordingly. We are hopeful that our revised manuscript could elucidate unclear points in our study, and make it suitable for publication in the World Journal of Gastrointestinal Oncology.

Reply to editorial comments:

Dear Editor:

Thank you very much for having considered our manuscript “Outcomes of neoadjuvant chemoradiotherapy followed by radical resection for T4 colorectal cancer” (manuscript NO: 58403), by Huang CM and colleagues. We are very happy to have received a positive evaluation, and we would like to express our appreciation to you and the Reviewers for the thoughtful comments and helpful suggestions. The point-by-point responses to the editorial comments are given below.

Query 1: I found the language classification was grade C. Please visit the following website for the professional English language editing companies we recommend:
<https://www.wjgnet.com/bpg/gerinfo/240>

Reply 1: As you requested, we have sent this manuscript to the English language editing company to thoroughly revise the grammar of this manuscript. Attached please find the certificate (O-2020-009176).

Query 2: I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any

approval document(s)

Reply 2: This was done accordingly and the approved grant application forms have been uploaded in the revision files.

Query 3: I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Reply 3: This was done accordingly and the original figure documents have been uploaded in the revision files.

Query 4: I found the authors did not write the “article highlight” section. Please write the “article highlights” section at the end of the main text.

Reply 4: We have now written the article highlight and this has been uploaded with the revised manuscript.

Reply to reviewer's comments

Dear Reviewers:

Thank you for your valuable comments and effort on our manuscript. We have made the changes and corrections to our article accordingly, and our point-by-point

responses to your comments are included below:

Reviewer 1 (reviewer's code: 00722050):

This is an outstanding manuscript with excellent data. However, two points need to be tackled by the authors. FOLFOX regimen needs to be clarified better also with literature historical and perspective data. Moreover, the authors report that partial organ resections were required when needed and the specimens were sent to the pathology department to ascertain the status of surgical margins. They also mention that two pathologists examined specimens and evaluated treatment response. In all these actions, the k-value of interindividual variability needs to be provided being this data crucial for the treatment response. Moreover, the authors need to mention if the pathologists used an ancillary tool (e.g., immunohistochemistry) to reach an agreement:

Query 1: FOLFOX regimen needs to be clarified better also with literature historical and perspective data.

Reply 1: Thank you for your valuable suggestions. Indeed, the FOLFOX regimen resulted in favorable tumor response following neoadjuvant chemoradiation in our study, and therefore the literature review of the regimen needs to be clarified. Please refer to the second paragraph of the discussion. In the paragraph, we reviewed several phase III randomized studies (the STAR-01 trial, the ACCORD 12/0405-ProDIGE 2 trial, the NSABP R-04 trial, and the German CAO/ARO/AIO-04 trial) on the efficacy of the FOLFOX regimen in the neoadjuvant treatment of locally advanced rectal cancer [J Clin Oncol 2011; 29(20): 2773-2780, J Clin Oncol 2010; 28(10): 1638-1644, J Clin Oncol 2014; 32(18): 1927-1934, Lancet Oncol 2012; 13(7): 679-687]. These randomized studies investigated the efficacy of FOLFOX versus fluoropyrimidine

administered concurrently with irradiation. Only the German CAO/ARO/AIO-04 trial demonstrated a positive impact of FOLFOX-based CCRT on improvement of pCR and disease-free survival [Lancet Oncol 2012; 13(7): 679-687]. The other three phase III randomized studies have revealed no significantly increased pCR rate between fluoropyrimidine-based and FOLFOX-based regimens. In our study, we extended the administration of FOLFOX before and after irradiation to maximize the neoadjuvant effect. The efficacy of extending FOLFOX was supported by many studies [J Clin Oncol 2016; 34(27): 3300-3307, Lancet Oncol 2015; 16(8): 957-966, J Clin Oncol 2006; 24(4): 668-674, J Clin Oncol 2010; 28(5): 859-865, Ann Surg 2011; 254(1): 97-102, Dis Colon Rectum 2009; 52(12): 1927-1934, Therap Adv Gastroenterol 2016; 9(5): 702-712]. The above papers are all cited in the second paragraph of the discussion.

Query 2: The authors report that partial organ resections were required when needed and the specimens were sent to the pathology department to ascertain the status of surgical margins. They also mention that two pathologists examined specimens and evaluated treatment response. In all these actions, the k-value of interindividual variability needs to be provided being this data crucial for the treatment response. Moreover, they authors need to mention if the pathologists used an ancillary tool (e.g., immunohistochemistry) to reach an agreement

Reply 2: Thank you for providing these insights. There were two independent pathologists to evaluate the treatment response. According to your suggestions, we performed kappa statistics to quantify and confirm the interobserver agreement. The κ value was 0.97, indicating an excellent agreement in this study. For any

discrepancy between the evaluations of the two pathologists, we consulted a third pathologist to solve the differences. Accordingly, we have added the related information into the Materials and Methods section on page 12 (lines 5-7) and page 13 (lines 7-8) as follows: “In the event of a discrepancy between the evaluations of the two pathologists, we consulted a third pathologist to resolve the differences.”; “We applied kappa statistics to quantify and confirm interobserver agreement.” We also have added the calculated κ value into the Results section on page 16 (lines 1-2) as follows: “The κ value was 0.97, indicating excellent interobserver agreement in this study.”

Reviewer 2 (reviewer's code: 03552518):

This is an interesting study reporting positive results of neoadjuvant chemoradiotherapy for locally advanced colon and rectal cancer. Neoadjuvant chemoradiotherapy is a common treatment for locally advanced rectal cancer with a complete pathologic response of 15-30% reported in many clinical reports. There is no consensus of neoadjuvant treatment for colon cancer. This study showed an improved R0 resection rate after neoadjuvant chemoradiotherapy both in rectal cancer and colon cancer. Their results may support the benefits of neoadjuvant therapy in the treatment of locally advanced colon cancer.

Reply: Thank you very much for the positive comments on the manuscript.

Reviewer 3 (reviewer's code: 03767436):

In my opinion, the overall level of the paper is very good structured: it is well written and several important considerations are highlighted. The discussion sections provide useful information for the readers and the conclusions appear rationale, emphasizing the needed to validate their data with further prospective randomized studies

Check the few spelling grammatical errors.

Reply: Thank you for your positive comments on the manuscript.

We sincerely appreciate your excellent comments. They have been very helpful to us in revising our manuscript so that it will hopefully be suitable for publication in the World Journal of Gastrointestinal Oncology.

Sincerely Yours

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