

Format for ANSWERING REVIEWERS

June 25, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 11142-edited.doc).

Title: The role of protective stoma in low anterior resection for rectal cancer: A meta-analysis

Author: Sheng-wen Wu, Cong-chao Ma, Yu Yang

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 11142

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

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) Reviewer 1: This well-conducted meta-analysis addresses a critical but controversial topic on the “protective stoma” in low anterior resection with TME for rectal cancer. Specific comments: 1. The nature of “meta-analysis” should be reflected in the title of the article. 2. The authors may justify why they only selected articles between 2007 and 2014. It seems that there are some relevant studies including a few well-designed studies that were carried out before 2007. Also, there a few meta-analyses on the similar or same topic, which should be mentioned and cited. 3. Overall, the manuscript is well presented and organized. However, there are many grammatical and stylistic errors, inappropriate use of abbreviations, and inappropriate expression of rephrases and sentences in the title, abstract and the main manuscript.

Response 1: Thank you! We have changed the title into “The role of protective stoma in low anterior resection for rectal cancer: A meta-analysis”.

Response 2: Thank you for your professional view. We only selected articles between 2007 and 2014 because we refer to a meta-analysis which was published in Hepatogastroenterology (Chen J, et al. Defunctioning stoma in low anterior resection for rectal cancer: a meta-analysis of five recent studies. 2012 Sep;59(118):1828-31.). In that study, author selected recent clinical trials from 2007 to 2011, so we updated the results on that meta-analysis. Therefore, we cited this article in the introduction.

Response 3: Thank you for carefully reviewing our manuscript. We had this manuscript copyedited by a

professional English editing service that specializes in scientific papers in shanghai and we checked the grammar again and again. We hope that the language of our manuscript has reached Grade A.

(2) Reviewer 2: The study lacks one of the most important risks for anastomotic leak: Neoadjuvancy or pre op Chemo and Radiotherapy. You should study your data and classify the patients in 2 groups: 1) with and 2) without radiotherapy and study the rate of anastomotic leakage with and without diverting stoma.

Response: Thank you for your professional view and valuable suggestion. Neoadjuvantchemoradiation therapy (nCRT) is increasingly being viewed as the gold standard for rectal cancer management. With the frequent use of nCRT for the treatment of locally advanced rectal cancer, there is growing interest in the application of sphincter preserving surgery in low anterior resection for rectal cancer. Unfortunately, there are no RCTs or non-RCTs about comparing protective stoma with and without neoadjuvantchemoradiation therapy in low anterior resection for rectal cancer. However, we still agree with you that we should classify the patients in 2 groups: 1) with and 2) without neoadjuvantchemoradiation therapy in the future study.

(3) Reviewer 3: Thank you for allowing me to review this manuscript. This is a review that evaluates the role of a protective stoma in rectal cancer surgery. The authors performed a literature review from 2007 to 2014. 11 studies were included (3 RCTs) with a total of 5612 patients. Comments: - The PRISMA guidelines for systematic reviews should be followed. More details on the excluded articles should be provided. - The manuscript needs English language revision. - Exclusion criteria should include non-rectal cancer proctectomy given your title. Did you also consider adding a minimum of patients to avoid small studies and case series? - The definitions of anastomotic leak should be included. - It would be interesting to know the incidence of anastomotic leak according to level of anastomosis, type of anastomosis (stapled (single or double), handsewn), laparoscopic vs. open, neoadjuvantchemoradiation, tumor stage, and other high-risk patient-related factors (DM, malnutrition, immunosuppression). - To further enhance this manuscript, details regarding the type of fecal diversion and indications for fecal diversion in the non-RCTs should be included. - P values should be added to table 1. - Figures are very helpful. - Not sure that you can conclude that a protective stoma actually DECREASES anastomotic leak but rather decreases its clinical manifestations and need for reoperation. - Overall I think the 2

findings of this study are limited by the narrow literature search and biased by the heterogeneity of the studies reviewed. Adding outcomes such as intra-abdominal abscess, other surgical morbidity, and mortality would further enhance the manuscript as well.

Response: Thank you for your critical and professional comment. We followed the PRISMA guidelines for systematic reviews. 132 studies were excluded because they were not related to the current study. 56 were reviews, 35 were case reports, 11 were animal studies and 20 did not meet the inclusion criteria. Upon further review, 14 were excluded because they were studies without comparative data. Then we evaluated 18 potential candidate studies in full text, 7 were not published in English. Finally, 11 studies were included in this meta-analysis. We added non-rectal cancer proctectomy in the Exclusion criteria. Anastomotic leakage was defined as a communication between the intra- and extraluminal compartments owing to a defect in the integrity of the intestinal wall at the anastomosis between the colon and rectum or the colon and anus. The definition of anastomotic leak was added into the introduction.

We would like to express our sincere thanks to you for your valuable suggestion, which is beneficial for strengthening our manuscript. Such as the incidence of anastomotic leak according to level of anastomosis, type of anastomosis, laparoscopic vs. open, neoadjuvant chemoradiation, tumor stage, and other high-risk patient-related factors. But unfortunately, there are no studies compare these factors with or without protective stoma in low anterior resection for rectal cancer. However, we will discuss the safety and efficacy of ileostomy and colostomy in a low anterior resection for rectal cancer by comparing the postoperation complications, then to investigate which type of stoma is better.

(4) Reviewer 4: Major issues -The major drawback of this meta-analysis is that RCT and non-RCT have been analyzed together. In non-RCT, use of allocation mechanisms other than concealed randomization means that groups are unlikely to be comparable. These potential systematic differences cause selection bias which produces imbalances in prognostic factors associated with confounding. Two separate meta-analyses should be conducted one for RCT and a second for non-RCT. The estimates of these two analyses can be compared by the z-score test. -A second major issue is the observed heterogeneity ($I^2=77\%$). This number discloses that studies were heterogeneous and the Random effects model should have been performed than the Fixed effects model. Additionally, authors do not make clear the percentage of heterogeneity in each of the two outcomes (anastomotic leak – reoperation). -A third major issue is that authors have not addressed confounding. Meta-regression analysis is a power tool to

counter bias introduced from confounding by producing 'adjusted' estimates of intervention effects: e.g.: single institution versus multi-institutional study, more sample size vs. less sample size study, community versus university hospital study e.t.c. -Besides, there is an already published meta-analysis [Ann Surg. 2008 Jul;248(1):52-60] including 27 studies (4 RCT) coming to same conclusions: A defunctioning stoma reduces the rate of clinically relevant anastomotic leakages and is thus recommended in surgery for low rectal cancers. -Table 1 should give the observed leak and reoperation percentages clearly. The observed risk ratio would be more digestible by the readers and be put in a proper clinical base. Minor issues -The first paragraph of the results contains duplicate information to figure 1. -The last paragraph of the results should be transferred to the discussion.

Response: Thank you for your critical and professional comment. This meta-analysis has presented only two outcomes; those with heterogeneity should be viewed with some caution. The heterogeneity among the studies should be taken into account in interpreting the results. First, there were only three RCTs, and data of RCTs and non-RCTs were not complete for both of the two outcomes. It lacked power for some complications of interest because of the small sample size and relative rarity of the outcomes. Second, among the studies included in the analysis, some studies included the small number of patients with different case selection and different diagnoses. As a result, it was not possible to perform subgroup analysis, and thereby, the clinical relevance of summary statistics might have been diminished. Despite the absence of randomized controlled trials, meta-analysis is still an effective way to make a comprehensive evaluation of existing quantitative results in high quality of non-randomized controlled trials. Therefore, we analyzed RCTs and non-RCTs together. In this present meta-analysis, the heterogeneity ($I^2=77\%$) discloses that studies were heterogeneous and the random effects model should have been performed than the fixed effects model. The last paragraph of the results was transferred to the discussion.

Frankly speaking, we acknowledged that there is an already published meta-analysis [Ann Surg. 2008 Jul;248(1):52-60] on this topic; however, it was published six years ago. Moreover, there are some highlights and updates in our manuscript. Over the past few years, there were a few well-designed studies on this topic, and we added these new studies in our present meta-analysis. At last, there were three RCTs and eight

non-randomized studies with a total population of 5612 patients, of whom 2868 had a protective stoma and 2744 did not. This was the largest sample size of meta-analysis, which reduces the publication bias, increases the power, and thus makes the conclusion more reliable. Therefore, we believe that our meta-analysis is of significant value on the topic.

(5) Reviewer 5: The manuscript/meta-analysis has several major limitations. It is limited to 2 outcomes leak and reoperation after LAR in rectal cancer rather than assess the benefit of stoma in more broad aspects including total morbidity and mortality. This is a complex setting and more thoughtful analysis is needed. The authors selected very simplistic approach to the issue of creating stoma looking at selected outcomes. This is very suboptimal data to me and the conclusions may be overstatements since other problems can occur with stoma creation including additional cost of 2nd surgery, hospital days. 1. Change title to more clear - The role of protective stoma.... for rectal cancer. A metaanalysis. - This is a metaanalysis. 2. Include more important data on mortality and total morbidity if available even lower number of studies 3. provide more detailed analysis of excluded studies 4. broad research with more than 90% irrelevant papers (poor criteria selection to start with). no need to mention those papers. Focus on 32 full text analysis 5. Needs improved wording and language. Ex. Stoma placed 'after' LAR.- the stoma is placed at the time of surgery. 6. Abstract section results- the sentence 4 does not make any sense. There was no obvious between study.... This is repeated in the body of the paper. 7. Review all papers again and run additional data and outcomes.

Response 1: Thank you! We have changed the title into "The role of protective stoma in low anterior resection for rectal cancer: A meta-analysis".

Response 2: Thank you for your professional view and valuable comment, which is beneficial for strengthening our manuscript. Unfortunately, there are only two studies compared other morbidity, so it cannot be analyzed in this present analysis.

Response 3: We appreciate your critical comment. We have provided more detailed analysis of excluded studies in the results of study characteristics.

Response 4: Thank you for your critical and professional comment. We followed the PRISMA guidelines for systematic reviews and search strategy, 132 studies were excluded because they were not related to the current study. 56 were reviews, 35 were case reports, 11 were animal studies and 20 did not meet the inclusion criteria. Upon further review, 14 were excluded because they were studies without comparative data. Then we evaluated 18 potential candidate studies in full text, 7 were not published in

English. Finally, 11 studies were included in this meta-analysis.

Response 5: Thank you for carefully reviewing our manuscript. We had this manuscript copyedited by a professional English editing service that specializes in scientific papers in Shanghai and we checked the grammar again and again. We hope that the language of our manuscript has reached Grade A.

Response 6: Thank you for your professional view and valuable comment. We have changed the Abstract section results- the sentence 4 into "The result indicated that the creation of a protective stoma in low anterior resection significantly reduces the rate of anastomotic leakage and the number of reoperations related to leakage".

Response 7: Thank you for your critical and professional comment. We have checked our paper again and again.

(6) Reviewer 6: This is a meta-analysis study on the necessity of protective stoma in low anterior resection with TME for rectal cancer. Its publication seems important in a time of intense and controversial discussion about the necessity of protective stoma in low anterior resection with TME for rectal cancer.

Response: Thank you for carefully and patiently reviewing our manuscript.

3 References and typesetting were corrected

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

Sincerely yours,

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