Dear Dr. Ma,

Thank you and the Reviewers for providing the critical comments on our manuscript entitled "Prognostic Value of Preoperative CEA/Tumor Size in Rectal Cancer" (No: 47249). It is with great pleasure that we have the opportunity to resubmit the article for further consideration. We have incorporated changes that reflect the detailed suggestions you and the reviewers provided. We also hope that our revision and the responses we provide below satisfactorily address all the issues and concerns you and the reviewers mentioned.

Review #1: You should design a prospective large-scale study since you have validated the values in the training cohort. Additionally you should maintain a longer follow-up period for rectal cancer since 3-years are not adequate to have safe conclusions for DFS (disease free survival and OS (overall survival), a fact considered as a bias when estimating Kaplan-Meier curves, and it is not refereed in the discussion section of this manuscript. You should probably have followed-up patients from 2012 further and not until 2016 as you present. I believe that this point should either be set as cut-off point in your study, but this might create a small sample size, or you should prolong the follow-up period, or present an adequate explanation in the discussion section of your manuscript. Your ideas are original and well-documented.

Response: We appreciate the time and effort the reviewer has dedicated to providing insightful feedback on ways to strengthen our study.

1. You should design a prospective large-scale study since you have validated the values in the training cohort.

Response: we thank the reviewer for encouraging us to conduct further prospective study. The current retrospective study will provide an important basis for us to carry out a prospective study. We have addressed this issue in

the discussion part of the revised edition. In addition, we wish we can conduct the prospective study in the future as the reviewer suggested.

2. Additionally you should maintain a longer follow-up period for rectal cancer since 3-years are not adequate to have safe conclusions for DFS (disease free survival and OS (overall survival), a fact considered as a bias when estimating Kaplan-Meier curves, and it is not refereed in the discussion section of this manuscript. You should probably have followed-up patients from 2012 further and not until 2016 as you present.

Response: we thank the reviewer for this critical comment. In our study, the follow up time varied from 3 years to 10 years and the median follow up time was 51 months. We have discussed this limitation in the discussion part of the revised edition.

3. I believe that this point should either be set as cut-off point in your study, but this might create a small sample size, or you should prolong the follow-up period, or present an adequate explanation in the discussion section of your manuscript.

Response: we thank the reviewer and have presented an explanation in the discussion section of our revised edition.

Review #2: The training and validation cohort couldn't be understood only by the abstract, what are the meanings of them? If those terms will be used, then you should make clear in the abstract. In introduction part; you should discuss why you need an adjustment by using tumor size. In addition, you should add more references for this hypothesis. You should also discuss why you selected only rectum cancer and not colon cancers. In methods section, you don't have to declare the number of patients, it should be present in "results" section. In methods section, it was still not understood why you study with two cohorts. Why did you use only "training cohort" for

determining a cut of value? You excluded the patents history of neoadjuvant chemo, did you also exclude the ones who had neoadjuvant radiotherapy? What Was the selected diameter, radiological or pathological? In results section, The metholodology starting with "According to the univariate analysis, age, TNM stage, differentiation, lymphovascular invasion,…." Should be discussed in methods section. The discussion section should be revised and more information about the prognostic efficacy of lab workup should be added.

Response: We thank the reviewer for the critical summarizations of our manuscript and the positive comments.

1. The training and validation cohort couldn't be understood only by the abstract, what are the meanings of them? If those terms will be used, then you should make clear in the abstract.

Response: We apologized for making the reviewer confused. We have clarified this issue in the abstract of revised edition.

2. In introduction part; you should discuss why you need an adjustment by using tumor size. In addition, you should add more references for this hypothesis.

Response: We thank the reviewer for this comment. We have added some explanation and references in the introduction part of our revised edition.

3. You should also discuss why you selected only rectum cancer and not colon cancers.

Response: We thank the reviewer for the comments.The current study pays more attention to rectal cancer since the incidence of rectal cancer is higher than that of colon cancer in China, which has been stated in the introduction part of our revised edition. Besides, the database of rectal cancer in our

hospital is more completed and more abundant.

4. In methods section, you don't have to declare the number of patients, it should be present in "results" section.

Response: We thank the reviewer for this suggestion and have revised the text in method section.

5. In methods section, it was still not understood why you study with two cohorts. Why did you use only "training cohort" for determining a cut of value?

Response: We apologized for making the reviewer confused. We used training cohort and validation cohort for one round of cross-validation, which is a simple model validation technique for assessing whether the result of a statistical analysis can be applied to another data set. In our study, the training cohort is used to generate an optimal cut-off point and validation cohort was used to test the applicability of this cut-off point and the model. This method is not uncommon in survival analysis, such as the studies of Smith et al. (Clin Cancer Res, 2015) and Rong et al. (World J Gastroenterol, 2018). We have clarified this issue in the abstract and method section of our revised edition.

6. You excluded the patents history of neoadjuvant chemo, did you also exclude the ones who had neoadjuvant radiotherapy?

Response: We thank the reviewer for this critical comment. Patients with neoadjuvant radiotherapy had also been excluded for the same reason. We have corrected this negligent mistake and changed the "neoadjuvant chemotherapy" into "neoadjuvant chemotherapy and/or radiotherapy".

7. What Was the selected diameter, radiological or pathological?

Response: We thank the reviewer for this critical comment. In our database,

both imaging and pathological data were recorded. Pathological data are preferred since the resected specimen are easier to measure. However, if the pathological data is missing, we would use the imaging data accordingly since the quality of imaging data was also high enough. We have clarified this issue in the method section of our revised edition.

8. In results section, The metholodology starting with "According to the univariate analysis, age, TNM stage, differentiation, lymphovascular invasion,…." Should be discussed in methods section.

Response: we thank the reviewer for this comment. In our current edition, we had stated the variable selecting method in the last paragraph of method section by using the following text: "Variables with a P value <0.10 in the univariate analysis were selected to fit the multivariate Cox model." In order to facilitate reading, we have made some adjustments to the text order in the method section of our revised edition.

9. The discussion section should be revised and more information about the prognostic efficacy of lab workup should be added.

Response: we thank the reviewer for this critical comment and we have added some information about the clinical value of CEA/tumor size and the possibility for clinical application in the discussion section of our revised edition.

Again, thank you for providing us the opportunity to improve our manuscript with your valuable comments and queries. We have worked hard to incorporate your feedback and hope that these revisions persuade you to accept our submission.

Sincerely yours,

Yan-Xin Luo, MD, PhD, Department of Colorectal Surgery, Guangdong Institute of Gastroenterology, Guangdong Provincial Key Laboratory of Colorectal and Pelvic Floor Disease, The Sixth Affiliated Hospital, Sun Yat-sen University, 26 Yuancun Erheng Road, Guangzhou, Guangdong, 510655,

China.

Email: luoyx25@mail.sysu.edu.cn

Telephone: +86-13826190263

Fax: +86-20-38254221