Response Letter to the Reviewers

Dear reviewers and editors:

Thank you for your efficient work in processing our manuscript entitled 'Nomograms and risk factor score prediction models for predicting OS and DFS in locally advanced rectal cancer with neoadjuvant therapy' (MS Number: 58981.v1). We are also very grateful to the reviewers for their important advice, which was helpful for improving the quality of our work.

In addition, we have carefully revised our paper based on the reviewers' comments, and the point-to-point responses are presented below:

Review report No. 1

Comment 1: High mortality rate and low compliance for adjuvant chemotherapy for patients with locally advanced rectal cancer remain a concern. In the era of treatment individualisation and the possibility of neoadjuvant therapy intensification, nomograms for survival can help clinicians to addopt therapy according to patient's individual risk. In the present retrospective cohort study on 220 patients the authors explored the prognostic value of risk factors on OS and DFS. Further, they build two nomograms and two risk factors prediction models to predict survival time and they also validated them. The article is well written, data clearly presented and sample size big enough to make relevant conclusions. I agree with the authors about the limitations to the study.

Response: Thank you very much for your efforts and advices. There are some tiny places to be improved. I will modify a little and look forword to your more advices. Thank you!

Review report No. 2

Comment 1: Introduction: "Therefore, achieving a pCR is closely related to the need for follow-up treatment." What do you want to say? What is a follow-up treatment?

Response: Thank you very much for your question because our writing mistake caused confusion. For “follow-up”, we mean surgical treatment and adjuvant therapy. We changed the wording to “subsequent treatment” in our revised article. Thank you again for reviewing the article.

Comment 2: Therapy: “There are three chemotherapeutic regimens available following radiotherapy” Are you talking about adjuvant therapy?

Response: Thank you very much for your question. In our study, 146 (66%) patients had received adjuvant therapy; therefore, we described the regimens following radiotherapy. We added an explanation of the adjuvant therapy to our revised article. Thank you again for reviewing the article.

Comment 3: Therapy: “The long-course regimen for radiotherapy comprised a total radiation dose from 45.0-50.5 Gy” Was chemotherapy delivered at the same time? Do you have any protocol to decide between short and long course radiotherapy?

Response: Thank you for this question. There were two radiotherapy regimens; for the long course, the total radiation dose ranged from 45.0 to 50.5 Gy, and for the short course, the total radiation dose was 25 Gy. All treatments were determined by the patient condition. We added an explanation to our revised article. Thank you again for reviewing the article.

Comment 4: Therapy: “All the patients received TME treatment approximately 2-60 weeks after NT based on the patients’ physical condition.” The interval range is different in table 1 in both groups.

Response: We really appreciate that this was noted. We used SPSS to randomly divide the patients into the primary group and the validation group; therefore, there was a difference in the

time interval between the two groups after neoadjuvant therapy. The mean time interval between the two groups was greater than 10 weeks, and the difference was not significant, so we retained this in the revised article. Thank you again for reviewing the article.

Comment 5: Follow-up: “Clinical data was obtained from follow-up visits conducted by telephone or email. For each follow-up visit, a medical history was collected, and a complete physical examination was carried out.” By phone, email… complete physical examination?

Response: Thank you for your question. In our study, all clinical data were obtained from patients who visited the outpatient clinic. All physical examinations were carried out in our hospital, and we utilized phone or email to determine the survival condition of the patients. We added an explanation to our revised article. Thank you again for reviewing the article.

Comment 6: Results: 137 deaths out of 155 patients. How can you explain this high mortality in patients who underwent radical treatment in stage II and III rectal cancer?

Response: Thank you so much for your question. There was a mistake in the death data. We changed this error in table 1. Thank you again for reviewing the article.

Comment 7: Results: Disease recurrence cannot be considered a prognostic factor. “…the more positive lymph nodes that are harvested, the higher the survival rate becomes.” How can you explain that issue?

Response: Thank you for your pertinent question. We mistook recurrence as a prognostic factor for OS in the analysis. We readjusted the factors with potential prognostic value for OS and utilized LASSO and Cox regression to screen the prognostic factors again. LASSSO regression selected 9 prognostic factors: Vascular_tumors_bolt, operation time, cancer nodules, yN, ypTNM,

body mass index (BMI), matchmouth distance from the edge, nerve aggression and postoperative CEA. After Cox regression of the factors, operation time and ypTNM were removed. Therefore, 7 prognostic factors were included in the nomograms and predictive model: Vascular_tumors_bolt, cancer nodules, yN, BMI, matchmouth distance from the edge, nerve aggression and postoperative CEA. The number of positive lymph nodes is not a prognostic factor in our new nomogram and prediction model. We made these changes in our revised article. Thank you again for reviewing the article.

Comment 8: Table 1: Too long and dense, you must divide data at least in two tables and organize clearer. There are several mistakes, ie: 9 patients M1, no stage IV patients.. Recurrences: local or distant Grammatical and syntax errors should be corrected.

Response: Thank you for your valuable advice. We divided Table 1 into 4 tables and corrected the errors in Table 1-4. Thank you again for reviewing the article.

Finally, we really appreciate your hard and efficient work. Every piece of advice is truly important for improving the quality of our work.

With kind regards,

Yours sincerely,