Author’s response to reviews

Title: A Modified TNM Staging System for Non-Metastatic Colorectal Cancer Based on Nomogram Analysis of SEER Database

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Author’s response to reviews:

Dear editor and reviewers,

Sincerely thank you for your kindly advices for our manuscript. Here is A point-by-point response letter. This letter provides a detailed response to each reviewer/editorial point raised, describing exactly what amendments have been made to the manuscript text and where these can be viewed.
George Karagkounis (Reviewer 1):

1. My major criticism is the continuous referral to the previously published T-plus system. The authors argue that they used the methodology described in this manuscript to improve on their previously reported T-plus system. Therefore, this manuscript would become more direct and clear by focusing on the Nomo-staging system alone and compare that to the AJCC system, which is the standard. Having repeated three-way comparisons that include the T-plus system does not not add something novel, is confusing and in the opinion of this reviewer, detracts from what is new in this manuscript.

Reply: Thank you for this advice. In the revision edition, we removed all results of the T-plus staging system evaluation in both Abstract and Results. All of the Tables and Figures were also revised.

2. Why did the authors decide to proceed with 5 stage groups, as opposed to 7 (similar to the AJCC staging)? Currently, the AJCC has a IIA, IIB and IIBC, yet the decision was made to group them into one. While this is not necessarily a flaw, it would be worth explaining the exact rationale.

Reply: Thank you for this advice. Finding a simple, less-group model is the first step to obviously disclose survival paradox. It would also be convenient to compare different staging systems' performance. In our previous study, we classified 25 TN combinations into 5 stage groups. Five stage groups makes the staging model simplest to analyze while still retain the survival paradox. We have been applying this 5-stage-group model in our previous two articles (Ref 4 and 5 in the manuscript). Therefore, in this study, we continued to apply 5 staging groups. Additionally, we admitted that to predict colorectal cancer prognosis more precisely and individually, more subgroups were needed. But the fundamental goal of construction nomo-staging system was to verify the concept of reconsidering the weight of lymph nodes status in prognosis prediction, instead of directly applying nomo-staging system into clinical practice. We added this explanation in the Methods (page 7, line 6) and the end of discussion (page 12, line 29):
Methods (page 7, line 6):

"After ranking the average standardized nomo-score, we planned to divide the 25 TN combinations into five groups (I, II, IIIa, IIIb and IIIc) to be in consistence with previous studies[4, 5]. As we found 5 stage groups would make the staging model simplest to analyze while still retain the survival paradox."

Discussion (page 12, line 29):

"In addition, the fundamental goal of construction nomo-staging system was to verify the concept of reconsidering the weight of lymph nodes status in prognosis prediction, instead of directly applying nomo-staging system into clinical practice."

Meanwhile, we also explained it, which was emphasized as the third shortcoming, in the discussion section in detail (page 12, line 19):

“The third shortcoming was that the Nomo-staging system was only separated to five groups because of the convenience when comparing the performance of the two staging systems by the same number of subgroups. To predict colorectal cancer prognosis more precisely and individually, more subgroups were needed. Moreover, studies have shown that molecular types could predict the prognosis of colorectal cancer independent of the TNM staging system[24-26]. Integrating the prognostic molecular markers, such as microsatellite instability, Ras and Braf gene mutational status and immune-score etc., into the prognosis prediction system may predict the prognosis of colorectal cancer more precisely."

3. The number of patients in each stage, both for the AJCC system and for the Nomo-system should be detailed to offer an estimate of how stages are distributed in each individual system.

Reply: Thank you for this advice. The number of patients in each stage, both for the AJCC system and nomo-system in SEER datasets and SAHZU database has already listed in the supplement Table1 (Table S1) and Supplement Table2 (Table S2).
4. The study's conclusions are clearly limited by the lack of long term follow-up for most patients. Even though this is mentioned as a limitation, it should be emphasized in the conclusions too. 3 year survival may be too short to definitively assess this system in colon cancer.

Reply: Thank you for this advice. In the revision edition, firstly, we performed an external validation on our own cohort (SAHZU database) with a median follow-up of 56 months. The validation confirmed the nomo-staging system could correct survival paradox between stage II and stage IIIa (see in Figure 4).

And admitting that 3 year survival may be too short to definitively assess this system in CRC, the Conclusion has been revised (page 13, line 5 and page 13, line 13):

"The present study established a modified TNM staging system via nomogram analysis which performed better than the 7th edition TNM staging system in predicting survival of non-metastasis colorectal cancer, which was both validated in SEER testing set and SAHZU database."

"However, the robust and rationality of increasing T-stage weight in staging system should be validated in more database considering the limitation of short follow-up time."

5. The authors, during their previous study on T-plus staging, used a Chinese cohort for validation. Did they attempt the same for this system? The generalizability of these findings is difficult to establish without validation.

Reply: Thank you for this advice. In the revised manuscript, we performed an external validation on our own cohort (SAHZU database, 1194 colorectal cancer patients) with a median follow-up of 56 months. The Kaplan-Meier curves showed the nomo-staging system revised survival paradox between stage II and stage IIIa by (see in Figure 4). The Abstract, Methods and Results were also revised accordingly (listed below in detailed).
Abstract (page 3, line 12 and line 18):

"And an external validation was performed on database from the Second Affiliated Hospital of Zhejiang University (SAHZU)."

"and the external validation in SAHZU database also showed distinctly better discrimination."

Methods (page 5, line 24):

"Total 1,194 patients were enrolled from a database of the Second Affiliated Hospital of Zhejiang University (SAHZU) for external validation. All patients were diagnosed with colorectal cancer between 2005 and 2011 by histopathological examination. Detailed and sufficient pathological survival information was extracted. Exclusion criteria were death by surgical complications within a 3-month postoperative period, stage 0 or stage IV disease, multiple colorectal cancer, or prior history of malignancy."

Results (page 8, line 19; page 9, line 18):

"A total of 1,194 patients were enrolled from the SAHZU database. The baseline characters were listed in Table S2. The median follow-up was 56 months (IQR=25 months)."

"The external validation of SAHZU database by Kaplan-Meier curves clearly showed the survival paradox between stage II and stage IIIa in the 7th edition TNM staging system, while the nomo-staging system revised the monotonicity of gradients."

6. Some references need to be edited. Ref 4 does not appear to be relevant to what is cited in the text.

Reply: Thank you for pointing out this mistake. The Ref 4 has been verified by “Li J, Guo BC, Sun LR, Wang JW, Fu XH, Zhang SZ, Poston G, Ding KF: TNM staging of colorectal cancer should be reconsidered by T stage weighting. World J Gastroenterol 2014, 20(17):5104-5112.”
7. In Figure 2, the survival of the entire population appears to be much worse in the first 2 panels compared to the third one. In fact, while 4 out of 5 stages in figure 2 reach 50% survival, this does not occur with any of the stages in figure 3. How do the authors explain this? Again, perhaps having the number at risk could clarify this.

Reply: Thank you for this advice. Noticing the Y-axis was the survival probability. After modifying the staging system, the distribution of patients in each stage has changed (see in Table S1). Therefore, the survival probability might be different in different staging systems. In statistical terms, the overall survival Kaplan-Meier curve decreased more quickly than disease-specific survival Kaplan-Meier curve. Therefore, out of 5 stages in figure 2 reach 50% survival, while this does not occur with any of the stages in figure 3. It was ensured by Dr. Tian Yu and Prof. Li Jingsong from College of Biomedical Engineering and Instrument Science, Zhejiang University. In addition, we have added the number at risk in each Kaplan-Meier curves in the revised manuscript to clarify this (Figure 2, Figure 3 and Figure 4).

8. In figures 2 and 3, some survival curves appear to end at/near 50 months, at the same time point for multiple stages and in multiple systems. Is that inherent to the follow-up data available by SEER?

Reply: Thank you for this advice. The median follow-up of SEER database we extracted was 39 months (IQR=51 months) and we excluded patients with unknown survival. However, there is still censored data where patients lost follow-up after 50 months but still alive in their last follow-up before 50-months. Therefore, we are sure it is inherent to the follow-up data available by SEER. The raw data has been upload in the submission system, the baseline of SEER database and the distribution of patients in different stage could be seen in Table S1.

Ioannis Hatzaras (Reviewer 2):

1. I am curious why the opted to use 5 staging groups, as opposed to 7 (per AJCC). They should elaborate on this in the methodology.

Reply: Thank you for this advice. The answer was same with Question 2 of the reviewer 1.
2. The follow up time is somewhat limited. They report 3 year survival, but in a disease with favorable 5 year prognosis. They should report this as a significant weakness, and perhaps employ a statistical modulation to address this.

Reply: Thank you for this advice. The answer was same with Question 4 of the reviewer 1.