Peer Review File

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Reviewer A:

Comment 1: A study of whether neoadjuvant chemoradiotherapy is effective for stage IIA rectal cancer. Although this is a retrospective study, the design of the study is good, as the patient background is adjusted by propensity score matching. The sample size is large and the level of evidence is high. In conclusion, compared with surgery group, neoadjuvant chemoradiotherapy + surgery + chemotherapy group had a better overall survival, furthermore, In the high-risk group, the Kaplan-Meier analysis showed that patients treated with neoadjuvant CRT + surgery + chemotherapy had better OS than those treated with surgery alone

I think it is a very wonderful result!

Reply 1: Thanks to the reviewer for the comments on this article.

Changes in the text: No changes.

Reviewer B:

Comment 1: The introduction does not read completely clearly to me. At one point the authors write: "Considering that patients with stage IIA rectal cancer have better survival in the absence of neoadjuvant therapy, and that neoadjuvant therapy inevitably leads to short-term or long-term toxic..." This reads as if this is already well-established (in which case there would be no reason for this analysis). I think the authors aimed to convey that the evidence is mixed regarding the utility of neoadjuvant chemoradiation for stage IIA rectal cancer, however, I think the writing needs to be revised to reflect this and make a much stronger case for the implications from this analysis.

Reply 1: We have to admit that this description could make people confused. We removed these confusing sentences and added some other evidence to show that the evidence on this issue was mixed.

Changes in the text: We have modified our text as advised (see Page 5, Line21- Page 6, Line2).

Comment 2: I would appreciate the authors specifying what SEER data is used for this analysis. The current SEER dataset goes until 2018/2019, so it's not clear why this analysis would only include data through 2015 (unless the authors used a specific SEER dataset, such as Patterns of Care, in which case they should state this).

Reply 2: We also considered the time period of inclusion when designing this study. We chose 2015 instead of 2018/2019, mainly considering the relatively good prognosis of patients with stage IIA rectal cancer, and we wanted most patients to have sufficient follow-up time (at least 3-5 years). So, we only included patients up to 2015. And we add the database name in the text.

Changes in the text: We added the name of the database (see Page 7, Line1-2).

Comment 3: In the "result measurement" sub-section of the methods section, it is stated that "ethnicity" will be examined (presumably as a potential covariable/confounder), however, it is

not referred to again in the results or the tables and it appears as if only “race” was used in the analyses.

Reply 3: We felt sorry that we may have used the wrong word. We supposed to use “race” instead of “ethnicity” in the “result measurement” section, as we did in the results. We modified this word in the text.

Changes in the text: We have modified our text to correct the improper word (see Page 7, Line 17).

Comment 4: Could the authors explain why they underwent several different analyses and yet left out some key comparisons? For instance, what does the analysis comparing neoadjuvant CRT vs. surgery alone accomplish? Given that the guideline recommendations for stages II-III rectal cancer is neoadjuvant CRT and adjuvant chemotherapy, why was there no comparison between neoadjuvant CRT + surgery + adjuvant chemotherapy vs. surgery + adjuvant chemo? This comparison may more directly compare the efficacy of neoadjuvant CRT, especially when included in the group of analyses that are already presented.

Reply 4: We think this is a very good comment and help us find some key comparisons. As we did in our study, we have compared neoadjuvant CRT + surgery vs. surgery alone, and neoadjuvant CRT + surgery + adjuvant chemotherapy vs. surgery alone. Because our exclusion criteria excluded patients who did not undergo surgery, the data did not include patients who underwent neoadjuvant CRT alone. So, it will be difficult to compare neoadjuvant CRT alone (without surgery) vs. surgery alone. However, we added the comparison between neoadjuvant CRT + surgery + adjuvant chemotherapy vs. surgery + adjuvant chemotherapy in the Results part, and added some discussion.

Changes in the text: We have modified our text as advised (see Page 9, Line10-14; Page 10, Line13-21; Page 15, Line15-22).

Comment 5: It is unclear why the authors are discussing the ESMO guidelines for rectal cancer treatment when the analyses used US data? It might be more pertinent to the study to discuss the National Comprehensive Cancer Network’s clinical practice guidelines or the American College of Surgeons Commission on Cancer’s National Accreditation Program for Rectal Cancer (NAPRC) Standards.

Reply 5: We admit that it was inappropriate. So, we add some comments about NCCN guidelines in the Introduction part and Discussion part.

Changes in the text: We have modified our text as advised (see Page 5, Line 14-17; Page 12, Line 17-20).

Comment 6: Somewhat related to the comment above – it seems to me that the overall results (i.e., abstract & conclusion) might be somewhat overstated for the findings of this paper. I think overall the results of these analyses are mixed. I think the sub-analyses are very interesting and it’s interesting/concerning that we can’t quite tell whether neoadjuvant CRT is helping everyone or not, but I don’t know if you can draw a definitive line one way or the other with the results presented here.

Reply 6: Thanks for the suggestions on the overall results and conclusions. We summarized the results according to the suggestions to make the results clearer.

Changes in the text: We have modified our text as advised (see Page3, Line20-Page 4, Line5; Page 17, Line 8-14).

Comment 7: Most of the references cited in this paper are a bit dated – are the authors sure that there have not been more recent publications related to this subject matter?
Reply 7: Although there are not too much studies on this topic recently, we have updated the literature as much as possible.
Changes in the text: We have modified our text as advised (see Reference part).

Reviewer C:

Comment 1: This is a retrospective study based on SEER database, including 14,505 stage IIA rectal cancer. However, although propensity score matching was applied to reduce selection bias, this type of study is not free from inherent limitation, and conclusion (recommendation) for patients with insufficient information does not seem useful. As the authors highlighted the limitation of their study, specific treatment information that can significantly influence overall survival had not been considered. Moreover, how the authors verify that radiotherapy or chemotherapy had been performed before or after surgery, which was not possible in the SEER database?
Reply 1: First, we strongly agree with this comment about limitations of this study. We don't have enough effective ways to eliminate these limitations. And we can only add them in the Limitations part. Second, for chemotherapy or radiotherapy before or after surgery, we can get data from the columns called "RX Summ—Surg/Rad Seq" and "RX Summ—Systemic/Sur Seq." in the SEER (Plus) database.
Changes in the text: We added some limitations in the text (see Page 16, Line 22).