Peer Review File

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Reviewer A

In this retrospective analysis by Huang, et al. the authors use LASSO regression to construct a nomogram to predict OS in patients with locally recurrent rectal cancer. The authors should be commended for taking on this challenging problem in this challenging patient population. Please find my comments below.

Major Comments:
The authors create a predictive model and present it as a nomogram. However, it is unclear how the authors intend to use this nomogram. Should this nomogram be used preoperatively to guide decision-making by patients? If so, then some of the variables need to be revised as they are only available postoperatively. Should the nomograms be used postoperatively to set expectations?
Reply 1: We appreciate the reviewer' question and have made revision to clarify the application of the nomograms.
Change in the text: We have made the change. **(See Page 6, lines 217, 218, and 219)**.

LASSO is a well-accepted form of subset selection, but I think a brief explanation is needed, especially for the audience of this clinical journal. It is not entirely clear to me how the subset was selected using LASSO and a brief explanation of this would be helpful.
Reply 2: We appreciate the reviewer' question and have made revision to explain the usage of LASSO.
Changes in the text: We have modified our text as advised **(See Page 3, line 88)**.

Authors state that M1/unknown status was an exclusion criterion but it clearly is a variable within the model. Please revise.
Reply 3: We appreciate the reviewer's suggestion. In the exclusion criteria of our manuscript, M1/unknown is for primary tumors, while M status is for recurrent tumors in the model. We have made corresponding modifications to avoid confusion.
Changes in the text: We have modified our text as advised **(See Page 3, line 69; Page 3, line 83; Page 4, line 119; Page 4, line 127; Page 6, line 211; Figure 3; Table 1;)**.

How is treatment gap different than time of recurrence? How is treatment gap defined? What is a positive CEA? Typically, CEA is reported as a numeric value and that probably has a much higher predictive value than "positive" or "negative".
Reply 4: We agree with the reviewer that our article did not well illustrate the definition of treatment gap and positive CEA. According to the SEER database, the treatment gap is the interval from the detection of relapse to the initiation of treatment, and the positive CEA is

defined as > 5 ng/ml (for smokers) and > 2.5 ng/ml (for nonsmokers). Indeed, the CEA in numerical form exists in the SEER database, but most of them are missing values, so we did not select this item.
Changes in the text: We incorporated the elaboration into the manuscript. **(See Page 3, line 75; Page 3, line 77)**.

MICE is a great technique for imputation, but it assumes variables are missing at random. Otherwise, this may introduce some bias. Was any analysis done to ensure that variables were missing at random? This should be in the limitations section otherwise.
Reply 5: We appreciate the reviewer's insightful suggestion and agree that it will make the article more rigorous.
Changes in the text: We have made the change in limitation section. **(See Page 7, line 229)**.

Pathologic stage II/III and M0/M1 status seem collinear. If a patient is stage II/III, they are obviously not M1.
Reply 6: We appreciate the reviewer's suggestion. However, the pathological stage is for the primary tumor, while the M stage is for the recurrent tumor, so there is no collinearity between them.
Changes in the text: Considering that the M stage of primary and recurrent tumors could be confused, we labeled the M stage of recurrent tumor as the M_{LRRC} stage. **(See Page 3, line 69; Page 3, line 83; Page 4, line 119; Page 4, line 127; Page 6, line 211; Figure 3; Table 1;).**

I would argue that it is pretty standard now for rectal cancer to be treated with neoadjuvant radiation (and more recently, with neoadjuvant radiation and chemotherapy – TNT). However, this was not always the case. I wonder if the long time period of analysis may actually introduce quite a bit of heterogeneity into the model. The way we treat rectal cancer in 2004 is quite different than the way we treat it in 2019. How is year of treatment accounted for in the model?
Reply 7: We agree with the reviewer that further elaborating on the effect of year of treatment would be helpful. The year of treatment leads to the difference in detailed treatment, such as the dose of radiotherapy and the pattern of neoadjuvant therapy. Detailed treatment of LRRC is still in exploration. At present, the treatment of LRRC is still based on surgery, and the role of perioperative treatment has not been determined. Therefore, we are looking forward to the results of several multi-center clinical trials, such as the PelvEx II. The difference in detailed treatment was not taken into account in our analyses, and have made revision in the limitation part.
Changes in the text: We have made the change in the discussion and limitation section. **(See Page 5, line 164; Page 7, line 230)**.

Not all M1 patients are created equal. A liver or lung metastasis is quite different than a brain or bone metastasis. Please comment on how this is accounted for in the predictive model.
Reply 8: This observation is correct and the SEER database has been updated in recent years to specify the site of metastasis. However, these data have not been updated in most LRRC. Meanwhile, the effect of different metastasis on LRRC survival was poorly studied. We add the imperfection in limitation and we will focus on this in future study.

Changes in the text: We have made the change in the discussion and limitation section **(see Page 6, line 181; Page 7, line 231)**.

There are several tense disagreements within the manuscript. This manuscript would benefit from grammatical review.
Changes in the text: We have made the revision in the manuscript. (**See Page 1, line 20; Page 1, line 24; Page 1, line 27; Page 2, line 35; Page 2, line 39; Page 2, line 40; Page 2, line 41; Page 2, line 42; Page 2, lines 43; Page 2, lines 44; Page 2, line 46; Page 2, line 47; Page 2, line 49; Page 2, lines 50, 51, and 52; Page 2, line 56; Page 2, line 59; Page 3, line 65; Page 3, line 80; Page 3, line 89; Page 3, line 90; Page 3, line 97; Page 4, line 114; Page 4, line 118; Page 4, lines 132 and 133**).

Minor Comments:
Please explain the abbreviations prior to using them. For example, LRRC is used without an explanation in the first paragraph of the introduction.
Reply 10: We have made the change.
Changes in the text: We have made the change. **(See Page 1, line 17; Page 2, line 38)**.

Page 2, line 8 is unclear: "including/without" have opposite meanings pertaining to definition of LRRC.
Reply 11: We thank the reviewer for pointing this out. We have made revision.
Changes in the text: We have made the change. (**See Page 2, line 58**).

Figure 1 is very helpful but is not referred to in the body of the manuscript.
Reply 12: We referred to Figure 1 in the manuscript. **(See Page 4, line 109)**.

Which R package was used for analysis? This should be included in the methods section.
Changes in the text: We agree and have updated. **(See Page 4, line 105)**.

P-values less than 0.001 can typically be reported as $p < 0.001$. Just a style point.
Changes in the text: We agree and have updated. **(See Page 4, lines 121-124; Page 5, lines 140, 144, and 146; Page 5, lines 172 and 179; Page 6, lines 185, 188, and 217; Table 1 and S2)**.

Reviewer B

Decisive comments to editors: I want to commend authors in the use of impressive statistical tools and in this review. SEER database, though powerful in numbers, can be lacking in strength in details. Its strength in tracking recurrences is particularly lacking, likely resulting in a handful of data for analysis. Author's methodology in patient selection is not fully clear. For example. SEER coding manual uses the following codes to describe invasive recurrences and their types:
13 Local recurrence of an invasive tumor
14 Trocar recurrence of an invasive tumor. Includes recurrence in the trocar path or entrance site following prior surgery.

15 Both local and trocar recurrence of an invasive tumor (both 13 and 14)
20 Regional recurrence, and there is insufficient information available to code to 21-27
21 Recurrence of an invasive tumor in adjacent tissue or organ(s) only
22 Recurrence of an invasive tumor in regional lymph nodes only
25 Recurrence of an invasive tumor in adjacent tissue or organ(s) and in regional lymph nodes (both 21 and 22) at the same time
These details are lacking in the manuscript and might play a significant role in the formulation of nomogram. Full disclosure of the patient selection process and details in the criteria is crucial for database review.

Reply 1: We appreciate the reviewer's suggestion. This new entry that the reviewer mentioned is valid for cases diagnosed January 1, 2022, and forward. There is no corresponding entry in the previous database.
We extracted LRRC from the SEER database with reference to the article by Daniel, V. T. The selection of LRRC was explained in the methods and a flow chart was drawn (Figure 1).
Reference: Daniel, V. T., Crawford, A., Kiefe, C. I., & Mahmoud, B. H. (2021). Recurrence and Mortality of Melanoma In Situ of the Trunk or Extremities: A Surveillance, Epidemiology, and End Results Analysis. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.]*, *47*(1), 1–5. https://doi.org/10.1097/DSS.0000000000002417

The internal validation methodology of randomly splitting cohort into training and test samples from the selected data set is interesting but lack external validation. If all patients in SEER data set are used to formulate the nomogram, and testing is done using existing patients' records, such comparison will provide a stronger case of support for the nomogram.
Reply 2: We agree with the reviewer that further elaborating on this point using new data would be helpful. However, considering that LRRC is still a minority group, external validation is still difficult. We are collecting corresponding information on LRRC from our center, and further studies will be conducted to support this model.

Comments to the authors: I want to commend authors in the use of impressive statistical tools and in this review. SEER database, though powerful in numbers, can be lacking in strength in details. When SEER database is used, the precise patient methodology and selection criteria should be fully disclosed to assure appropriateness of the patients and topics being studied and reviewed.
Reply 3: We appreciate the reviewer's suggestion. This new entry you pointed out is effective for cases diagnosed January 1, 2022, and forward and there is no corresponding entry in the previous database.
We extracted LRRC from the SEER database with reference to the article by Daniel, V. T. The selection of LRRC was explained in the methods and a flow chart was drawn (Figure 1).
Reference: Daniel, V. T., Crawford, A., Kiefe, C. I., & Mahmoud, B. H. (2021). Recurrence and Mortality of Melanoma In Situ of the Trunk or Extremities: A Surveillance, Epidemiology, and End Results Analysis. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.]*, *47*(1), 1–5. https://doi.org/10.1097/DSS.0000000000002417