Peer Review File

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Reviewer A

Comment 1: The manuscript is excellently written and very well structured.

Reply 1: Thanks a lot for your carefully review of our manuscript. Several published studies have shown that radical prostatectomy (RP) could prolong survival and be safely done in patients with metastatic prostate cancer (mPCa), but now it remains unclear which subgroups may benefit from this aggressive surgery. The purpose of our study was to develop a reliable model to identify ideal candidates for RP on a large population-based level. We hope this information could be complimentary to current literature.

Comment 2: There are some comments about the statistical analysis:

1) Lines 113-114: it is not advised to select significant variables based on univariable analysis. It is more advised to select all variables in the multivariable analysis based on previous literature. This selection procedure of variables enables more statistical bias. So please select variable at first based on available literature and then put all predictors of interest at once in a multivariable model.

Reply 2: Thank you very much for your comments and suggestions. In this revised version, we have made correction according to your suggestions. We included all variables based on available literature in the multivariable model for predicting CSM (such as age, PSA, Gleason score, T stage, N stage, and M stage). These data were listed in updated Table 2.

Changes in the text: see Page 5-6, line 115-120; Page 7, line 146-152.

Comment 3: Line 113: I do not understand why it was chosen to develop a model without patients treated with RP. I recommend to develop a model including all variables of interest and the treatment (RP vs NLT) to quantify if men treated with RP or NLT have more risk of CSM.

Reply 3: Thanks very much for your comment. Previous studies observed a survival benefit in men with mPCa and managed with RP. We tested the hypothesis that only specific mPCa patients would benefit from RP and that the potential benefit would vary based on tumor characteristics. Therefore, we aimed to establish a normogram for the prediction of cancer specific mortality (CSM) in mPCa patients who were treated with NLT. This normogram was then applied to identify the ideal candidates that can benefit the most from RP in the NLT patients. Here patients were stratified into three different risk groups (good, intermediate and poor). Our findings showed that RP could confer a survival benefit (cancer specific mortality rate) for the low-risk patients, rather than patients with an unfavorable profile at higher risk of CSM. This analysis reveals what we may already think, meaning that patients with a rather beneficial outcome, and with good prognostic features will certainly benefit more from RP, while those with a very aggressive course of disease will rather not.

Comment 4: Line 118: calibration curves are always perfect at internal validation and are not informative, so this can be omitted.
Reply 4: Thanks very much for your comment. In this revised manuscript, we have revised the relevant parts of the paper according to your suggestions. The calibration curve was omitted.
Changes in the text: see Page 6, line 121-127; Page 7, line 155.

Comment 5: The authors report the Harrel c-index for discriminative ability. It can however be advised to report the time-dependent-AUC to quantify the discrimination at a model for a particular time.
Reply 5: Thank you very much for your suggestions. In this revised manuscript, we performed area under the time-dependent receiver operating characteristic curve (AUC) to evaluate the discrimination ability of the model according to your suggestion. The AUC for the 1-, 3- and 5-year CSM was 0.624, 0.616 and 0.641, respectively, reflecting relatively favorable agreement in the probability of cancer-specific survival between the nomogram prediction and actual observation (Supplementary Fig.1).
Changes in the text: see Page 6, line 121-124; Page 7, line 154-155.

Comment 6: The authors dichotomous PSA, but it is better to leave continuous variables as it is.
Reply 6: Thank you very much for your comments. We have made correction according to your comment. These data were listed in updated Table 1 and 2.
Changes in the text: see Page 6, line 120-121.

Comment 7: In table 3 the authors report a hazard ratio. However, the hazard ratio is a relative effect and the baseline effect is not specified.
Reply 7: Thank you very much for your comment. Table 3 shows the effect of radical prostatectomy on cancer-specific mortality in different groups after adjusting for age, prostate-specific antigen (PSA), Gleason score, and tumor stage (T stage, N stage and M stage).

Reviewer B
Comment 1: I appreciate this study, but I suggest to improve your results showing:
1) Time to castration resistence in RP group.
Reply 1: Thanks very much for your comment. While previous studies reported on survival benefits and feasibility concerning RP there a currently no data available concerning a valid approach to detect patients that will benefit the most from RP. Our findings support that patient subsets with favorable oncological profiles at lower risk of CSM might benefit more from the removal of the primary tumor. This analysis therefore provides a significant impact for the scientific community**.**
1) The detailed information on systemic treatment and time to castration

resistence are not available in the SEER database. We have acknowledged it in the limitations section.
Changes in the text: see Page 12, line 267-268.

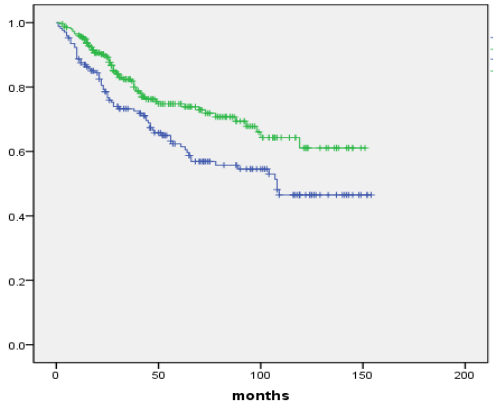
Comment 2: Number and site of metatstasis.
Reply 2: Thank you very much for pointing out our limitation. The detailed information about number and site of metastasis are not available in the SEER database (Since 2010, the SEER has only recorded metastatic spread to the lung, liver, bone, and brain), it would be associated with survival outcomes of mPCa patients. We have acknowledged it in the limitations section.
Changes in the text: see Page 12, line 267-269.

Comment 3: add results of oligometastatic Pts (mets <or = 5).
Reply 3: Thanks very much for your comment. As we mentioned before, detailed information on the extents of distant metastasis are unavailable in the SEER database. We have acknowledged it in the limitations section.
Changes in the text: see Page 12, line 267-269.

Comment 4: Define accurately role of Testosterone preoperative and during HT in predicting adverse pathological outcomes after rp(World J Urol. 2020 Jul 18. doi: 10.1007/s00345-020-03368-9. -Oncotarget. 2017 Mar 14;8(11):18424-18434. doi: 10.18632/oncotarget.12906.
Reply 4: Thank you very much for pointing out our limitation. The data on testosterone level are not available in the SEER database. We have acknowledged it in the limitations section.
Changes in the text: see Page 12, line 267-268.

Comment 5: Define QoL after RP and in LT population.
Reply 5: Thanks very much for your comment. As we mentioned earlier, due to limitations of the SEER database, we were unable to obtain information about patient performance status, comorbidities, complications and QoL of RP. We have acknowledged this point in the limitations section.
Changes in the text: see Page 12, line 265-266.

Comment 6: Describe impact of extended vs non-extended LAD in RP.
Reply 6: Thanks very much for your comment. In this cohort, we found that extended LAD could confer a survival benefit in mPCa patients who underwent RP when compared to non-extended LAD ($p = 0.005$). But we did not show these data in this paper, in order to make our study clearly report the impact of RP on the survival outcomes of mPCa patients.



Kaplan-Meier Survival Curves (extended vs non-extended LAD)