TCR TRANSLATIONAL CANCER RESEARCH
ADVANCES CLINICAL MEDICINE TOWARD THE GOAL OF IMPROVING PATIENTS' QUALITY OF LIFE
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Peer Review File

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Reviewer A

1. English language of the paper needs professional editing after revisions.

Reply1: Thanks for reviewer's suggestion. We have improved the readability of the paper using English editing service. Besides, the English editing certification was also submitted as attached file.

2. Abstract. In the background part, "in the debate due to the rarity" and "these associations" are unclear and inaccurate, and the latter should be the prognostic role. In the methods part, please also describe the data collection of other clinical covariates and how these patients were followed up. In the part of results, please provide HR values of these prognostic variables. The treatment benefits in patients with LNR>0.23 receiving POAT are not convincing, please test the interactive effects between the two variables in the statistical analysis in the main text. The conclusion should only repeat the main findings and please have comments on clinical implications.

Reply2: Considering the Reviewer's suggestion, we have corrected our sentence in the background part. In the methods part, clinic covariates collection was described more clearly in the revised manuscript. However, the details of followed up, such as "*how is the intervals between each follow up, what examinations have done at the follow up*", is lack in SEER database. We could only access the data of cause of death classification like "*Alive*", "*Dead (attributable to this cancer)*", and "*Dead (attributable to causes other than this cancer)*". In the results part, we have added HR and P-value for each risk factors. The interactive effects between LNR, POAT and other factors were analyzed using Cox regression model (**Supplemental table 1 and 2)**. Finally, the conclusion part was corrected according to reviewer's suggestions.

Change in the text: we have modified our text as advised (Page 2, Line 8-9, Line 13-16; Page 3, Line 6-12, Line 13-15, Line 18-19; Page 9, line 9-12, line 16-22, marked in red).

3. Introduction. This part is not informative. The significant predictive effect of LNR does not indicate it is necessary to replicate its predictive effect in HSCC. The authors must provide more insights on the necessity of the current research topic. In this part,

a brief review on predictor of poor gnosis of HSCC is needed. It is also essential to explain why studies on the prognostic factors of HSCC here.

Reply3: Thanks for reviewer's valuable suggestion. We have corrected the introduction part and clarified the necessity of our study. In the introduction section, the logic flow is "*Conventional N stage is not enough in HSCC → The number of positive LNs and LNR is related to prognosis of HSCC but LNR maybe more appropriate → Current studies regarding to prognostic value of LNR in HSCC still has many limitations, thus we should analyze it further*". We hope our answers could appropriately address the concerns of the reviewer.

Change in the text: we have modified our text as advised (Page 5, Line 6-13, marked in red).

4. Methodology. Although data sources of the study cohort have been described in this part, the authors should briefly describe the data source here. In this part, please describe how these patients were followed up.

Reply4: Thanks for reviewer's suggestion. We added the details of variable collection in the revised manuscript. Besides, we totally agree that how these patients were followed up is important. However, as is mentioned in Reply1, the details of followed up, such as "*how is the intervals between each follow up, what examinations have done at the follow up*", is lack in SEER database. We could only access the data of cause of death classification like "*Alive*", "*Dead (attributable to this cancer)*", and "*Dead (attributable to causes other than this cancer)*". Thus, we have added this limitation in the discussion section.

Change in the text: we have modified our text as advised (Page 6, Line 10-18, and Page 14, Line 15-17, marked in red).

5. Statistics. I suggest the authors to use mean and SD to describe variables with a normal distribution. For analyzing the predictive effect of LNR, please describe how the adjustment analysis was performed. The authors used ROC to define the cut-off value of LNR, making the determination of this cut-off value sample-dependent. I suggest the authors to use quartiles to re-validate the study findings.

Reply5: We have made correction according to the Reviewer's comments. Variable conforming to normal distribution is reported as mean and SD. Besides, the details of analysis regarding to the LNR and prognosis have been illustrated in the revised manuscript. Finally, in the univariate and multivariate analysis, we also used quartile of LNR (divided in =<0.179 and ≥0.179 group) as another factor to validate our

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findings.

Change in the text: we have modified our text as advised (Page 7, Line 7-10, Line 13-20, and Page 10, Line 12-16, marked in red).

Reviewer B

The influence of LNR on OS and CSS in hypopharyngeal SCC is of importance in our field. The manuscript is well written and clearly structured. Nevertheless, I struggle with the methods of the study. The authors included 391 hypopharyngeal SCC patients. They reported that all patients underwent neck dissection and 256 adjuvant radio or radiochemotherapy. They do not mention if the ND was performed uni- or bilaterally. Futhermore, they do not present data how many patients underwent adjuvant radiotherapy of the tumor region only and how many underwent irradiation of the neck. In my opinion this is highly important to examine the influence of surgical procedures as the neck dissection and pathological criterias as the LNR. Therefore, the authors have to methodological options: either they include only patients without adjuvant radiotherapy or provide data of the radiotherapy (region and dose). Furthermore, the grammar and style should be proofread by a native speaker.

Reply:

Thanks for reviewer's very professional suggestions. It is really true that reporting the details of LND and POAT is also important confounding factors in this study. However, the SEER database lacked the information on these aspects.

For one thing, we could not access the information on which region were performed LND. We admitted LNR could be affected by both LNs harvest during surgery and positive LNs number. Those with an insufficient LND during surgery could have caused risk overestimation of LNR. To ensure the quality of LND, we excluded the patients with less than 10 LNs examined, and finally included 391 patients for further analysis. We hope this method could largely minimize the bias of this study.

For another, the dose and regimen of the POAT were also unclear in the SEER database. We could only access the information such as the sequence (before or after surgery) and method (beam or implants) of radiotherapy. In this study, we aimed to investigate the prognostic value of LNR in HSCC. Although the region and dose of POAT could be a potential confounding factors affecting the prognosis, we believe that only including information of 'whether patients receive POAT or not' is also enough for multivariate analysis. Similar data handling methods could also be found in other studies in HSCC (1-3).

Besides, reviewer suggested that we could also choose to include only patients without adjuvant radiotherapy for further analysis. Firstly, we should apologize that

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we have made a clerical error. The truth is that 312 patients received POAT after surgery, which means only 72 patients without POAT in this study. We speculated that in the real situation, patients generally suspect LNs metastasis could receive sufficient LND. Therefore, the majority of these patients is in the high-risk group and would also receive POAT after surgery. The number of patients with not only sufficient LND but also without POAT is too small for us to analysis.

Finally, we thank again for reviewer's valuable suggestions. Please accept our apologies that we could not completely make changes according to the comments of the reviewers. These limitations have been illustrated in the discussion section. The manuscript has been edited by native speakers, and the certification was submitted as supplemental file.

Reference:

1. Heng Y, Zhu X, Zhou L, Zhang M, Li J, Tao L. A prognostic nomogram for predicting the long-term survival outcome of hypopharyngeal squamous cell carcinoma patients after tumour resection to assist the decision-making of postoperative adjuvant treatment. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2020;46(2):245-51.
2. Lin Z, Lin H, Lin C. Dynamic prediction of cancer-specific survival for primary hypopharyngeal squamous cell carcinoma. International journal of clinical oncology. 2020;25(7):1260-9.
3. Tang X, Pang T, Yan WF, Qian WL, Gong YL, Yang ZG. A novel prognostic model predicting the long-term cancer-specific survival for patients with hypopharyngeal squamous cell carcinoma. BMC cancer. 2020;20(1):1095.