Peer Review File

Article information: https://dx.doi.org/10.21037/jgo-23-905

Reviewer A

The paper titled "Clinicopathologic characteristics and survival analysis in esophageal neuroendocrine carcinoma: a propensity score-matched and nomogram analysis based on the SEER database" is interesting. ENEC and ESCC have distinct clinicopathologic characteristics. ENEC is associated with poor prognosis. Surgery, chemotherapy, and RT are beneficial for the survival in ENEC. The predictive model of nomogram showed an accurate and efficient predictive ability for patients with ENEC for prognostic factors. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) The abstract is not sufficient and needs further modification. The research background did not indicate the clinical needs of the research focus.

Reply: We have revised the abstract as requested.

Change in text: page 2, line 3-7.

2) Why did this study end in 2016? What has been the situation in the past five years? Suggest adding relevant content in the discussion.

Reply: Due to the potential for database updates to take several years, the latest cutoff date for the SEER database used in our article, at the time of writing, is 2016. We have incorporated recent literature on ENEC in the introduction section.

Change in text: page 4, line 10-20.

3) What factors are associated with low survival rate in ENEC patients? Suggest adding relevant content.

Reply: We added relevant content in "Discussion" part.

Change in text: Page 8, line 19-22.

4) What type of patients benefit most from the results of this study? What is the author's next research plan? It is recommended to add relevant content to the discussion.

Reply: We added some discussion and introduction of our own research in the "Discussion" section.

Change in text: Page 9, line 6-11.

5) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as "Clinicopathological and prognosis significance of RIPK1 in patients with cervical squamous cell carcinoma: a retrospective cohort study, Transl Cancer Res, PMID: 37304533". It is recommended to quote this article.

Reply: We enriched the introduction section and cited some relevant literature (Ref 11-14). But the recommended paper (Clinicopathological and prognosis significance of

RIPK1 in patients with cervical squamous cell carcinoma: a retrospective cohort study, Transl Cancer Res, PMID: 37304533) was not cited.

Change in text: Page 4, line7-34.

6) In the introduction of the manuscript, it is necessary to clearly indicate the knowledge gaps and limitations of prior study.

Reply: We added the knowledge gaps and limitations of prior study.

Change in text: Page 4, line 7-20.

Reviewer B

1) First, the title needs to indicate the comparisons of clinicopathologic characteristics and prognosis between ENEC and ESCC, as well the development and validation of a prognosis prediction model in ENEC.

Reply: We changed the title as "Comparison of Clinicopathological Features and Survival Analysis Between Esophageal Neuroendocrine Carcinoma and Esophageal Squamous Cell Carcinoma Based on the SEER Database, Alongside Nomogram Analysis for Esophageal Neuroendocrine Carcinoma"

Change in text: Page 1, line 2-5.

2) Second, the abstract needs some revisions. The background did not indicate the knowledge gaps on the two research focuses. The methods did not describe the inclusion criteria of ENEC and ESCC patients, how the clinicopathologic characteristics and prognosis were compared, how the training and validation samples were generated, and how the prognosis prediction model was developed and validated. The results need to describe the numbers and characteristics of the ENEC and ESCC patient cohorts. Please specify the outcomes of the two groups such as rates of liver metastasis, HR values for identified prognostic factors, and C-index in the validation sample. The conclusion should have more detailed comments for the clinical implications of the findings.

Reply: We made detailed revisions to the abstract section based on the suggestions.

Change in text: Page 2.

3) Third, the introduction of the main text needs an extensive review on what has been known on the clinicopathologic characteristics and prognosis of ENEC and the prognosis prediction models in ENEC, analyze the limitations and knowledge gaps of prior studies, and explain why the authors need to compare ENEC with ESCC.

Reply: We made detailed revisions to the introduction section based on the suggestions.

Change in text: Page 2, line 24-32 to Page 4, line 1-34.

4) Fourth, in the methodology of the main text, the authors need to specify the clinical research design, follow up procedures of the SEER cohort, the generation of training and validation samples, details of the analyses on the prognostic factors,

and how the predictors were selected for the prediction model. It is also important to describe the calculation of the predictive accuracy indicators and their threshold values for a goof prediction model.

Reply: We made detailed revisions to the method section based on the suggestions.

Change in text: Page 5, line 5, line 27-30, and page 6, line 3-13.

5) Finally, please consider to cite several related papers:

1. Yin Y, Han L, Chen Y, Ruan J, Zheng A. Vulvar neuroendocrine carcinoma: a case report and literature review. Gynecol Pelvic Med 2022;5:30.

2. Xia L, Lai J, Liu X, Kong F, Qiu S, Hu H, Zhu S, Cao J. Epidemiological and survival outcomes of neuroendocrine carcinoma of the breast: a SEER data analysis. Transl Cancer Res 2023;12(8):1951-1962. doi: 10.21037/tcr-23-368.

3. Qin J, Kang X, Li Y. Optimal management of locally advanced esophageal squamous cell carcinoma. Ann Esophagus 2023;6:36.

4. Shi ZZ, Jin X, Li WT, Tao H, Song SJ, Fan ZW, Jiang W, Liang JW, Bai J. Dihydroorotate dehydrogenase promotes cell proliferation and suppresses cell death in esophageal squamous cell carcinoma and colorectal carcinoma. Transl Cancer Res 2023;12(9):2294-2307. doi: 10.21037/tcr-23-136.

Reply: We added some references.

Change in text: We included the aforementioned references separately in the introduction section of the article as references 5, 15, and 16. Paper 4 has not been cited in the text.