Author’s response to reviews

Title: A modified M-stage classification based on the metastatic patterns of pancreatic neuroendocrine neoplasms: a population-based study

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The authors' response letter has been included as a supplementary file

Reviewer #1 Comments:

Comment 1

This is a descriptive retrospective data involving a reasonably large number of an uncommon condition. Generally, the language used proved to be quite challenging and made the reading difficult.

Author reply
Dear Dr. Rohana Ghani. We are sorry for the non-native language in last version. The revised manuscript been carefully revised by a native English editor.

Comment 2

Too many figures. Figures 2, 3b, 3d, 4b, 4d are redundant.

Author reply

Thanks for your critical comments. We have revised the manuscript and delete redundant figures.

Comment 3

The strength of this study is the large database. However, the main findings which include the sites of metastases, survival and predictors of metastases are well-known factors with the addition of Ki67 and hormonal levels.

Author reply

Thanks for your critical comments. We have re-analysis the raw data and re-written the manuscript. The main finding of the revised manuscript is we modified the AJCC and ENETS M-stage based on the metastatic patterns of pNENs. The Harrell’s concordance index showed the modified M-stage classification had superior discriminatory capability than the AJCC and ENETS M-stage classification.

Comment 4

Furthermore, the authors acknowledged that the accuracy of the report may be reduced by limited knowledge on other metastatic sites.

Author reply

As far as we know, the SEER program is an authoritative source of information on cancer incidence and survival in the United States. Unfortunately, for cancer metastasis, this program only included tumor metastasis to live, bone, brain, and lung. This is a limitation of SEER program and our manuscript.

However, consist with previous studies (Chamberlain et al. Am Coll Surg. 2000; 190: 432-445; Modlin et al. Cancer. 2003; 97: 934-959; Riihimäki et al. Int J Cancer. 2016; 139: 2679-2686), we also found liver is the most organ of metastasis. In the present study 96.12% pNENs with single organ metastasis presented liver metastasis and had better prognosis than the other
metastatic patterns. Thus, we modified the M-stage by spreading liver metastasis from the other metastatic pattern.

We think the mentioned limitation of SEER may be unable to influence the accuracy of our results, however, we still want to acknowledged the limitation of our manuscript.

Reviewer #2 Comments:

Comment 1

I would recommend that Author add the informations about function of the pNENs (functional vs unfunctional).

Author reply

Dear Dr. Maciej Kolodziej. Thanks for your useful suggestions; however, the SEER program did not classify pNENs into functional pNENs or unfunctional pNENs. Halfdanarson et al. (Ann Oncol. 2008 Oct;19(10):1727-33), have suggested that pNENs with histology codes 8151, 8152, 8153, 8155 could be defined as functional pNENs, and pNENs with histology codes 8150, 8240, 8241, 8246 could be defined as nonfunctional pNENEs; and We used this classification in our dataset, we found nonfunctional pNEN was a risk factor of metastasis, however, there was no static significant (nonfunctional vs. functional, OR = 1.883, P=0.058) (see the following table).

However, as mentioned by Halfdanarson et al., the SEER database did not offer information on symptoms at presentation. Thus, it is hard to accurately classify PNENs into functional pNENs or unfunctional pNENs. We only mentioned this issue in the discussion as following: Usually patients with pNENs, especially non-functioning pNENs, in the tail of pancreas are less likely to cause obstructive signs and hormonal symptoms until tumors extending to the peritoneum, spleen and distant organs. Thus, at the time of diagnosis, distant organ metastases exist in most of these patients.

Comment 2

I would recommend that Author add the informations about grading of the primary tumor according mitotic count and Ki-67 (NET G1, NET G2, NET G3 and NEC).

Author reply

Thanks for your suggestion. Unfortunately, the SEER database also failed to offer information about mitotic count and Ki-67. Thus we have discussed this issue as follwong: Unfortunately, SEER database did not record Ki-67 status and graded the primary tumor only on the basis of morphological description (ICD-O-3) in the pathology report. Thus, we failed to evaluate the predictive role of Ki-67 status and WHO 2010 grading classification (NET G1, NET G2, NET G3 and NEC) in distant organ metastasis.
Thanks again for your suggestions!