Peer Review File

Article information: http://dx.doi.org/10.21037/gs-20-634.

Reviewer A:

The manuscript by Liu et al uses the SEER database and their local hospital experience to examine the effect of age on characteristics and outcomes of patients with PNETs. The manuscript requires significant attention to English grammar.

Reply: Thanks for your reminder. We have seeked professional language editing service provided by AME Editing Service (AESE2020319), and the certification was attached to the supplementary material.

Comment 1: The authors indicate that early onset is associated with better prognosis. However, in their own series, this was not found to be true. While this could be an effect of a smaller sample size it could also indicate confounders in the SEER database that are not evident in the SEER database. Was any consideration given to looking at age distribution that might more readily reveal differences – for instance less than 40 vs >60?

Reply 1: Thank you for your kind reminder of the confounders in the SEER database. We did have considered giving look at age distribution that might more readily reveal differences- for instance less than 40 vs >60. However, we found the number of patients less than 40 was too small to conduct the research; and as indicated in the

manuscript, the average age at diagnosis of pNET in China was younger than that of SEER database, obviously, >60 was not suitable for the FUSCC cohort. Therefore, we chose 50 yrs old as the cut-off value. Anyway, we will continue to expand our cohort and the follow-up information in the future to exclude the effect of a smaller sample size.

Changes in the text: No.

Comment 2: The authors conclude that earlier resection is warranted for all patients. This statement is widely divergent from current recommendations for small PNETs where observation is considered a viable management option. Do the authors have data to support this conclusion?

Reply 2: Yes, for NF-PNETs that smaller than 2 cm, current recommendations are still not in consensus and observation is considered a viable management option. However, according to Haynes et al., even small tumors can have aggressive behavior and recommended resection. And as indicated by our study, EOpNETs have better prognosis than TOpNETs, therefore, it seems that once diagnosed of pNET, the sooner patients receive surgery, the better the survival rate. Meanwhile, even small tumors which need follow-up can cause significant discomfort and stress for patients and impact the quality of life at multiple levels. Therefore, we suggested that earlier resection is warranted for all patients with pNET.

Changes in the text: We have added the related content and highlighted it by using a different color in the manuscript.

Comment 3: Did the authors identify a reason as to why patients did not undergo resection? Was extent of disease too great or were there other medical factors that precluded resection?

Reply 3: Thank you for your question, it is very interesting. According to our experience, the extent of disease too great was one of the reasons, but the most common reasons were financial problems and the fear of relatively large surgery, especially for tumors located in the head and uncinate.

Changes in the text: No.

Reviewer B:

Comment 1: The heading in Table 1 on the left side of the table both say EOpNET. Presumably the larger one is meant to say TOpNET?

Reply 1: Thank you for kind reminder. We have revised this mistake in the resubmitted manuscript.

Changes in the text: We have revised this mistake in the resubmitted manuscript.

Comment 2: -50 yrs old cut-off is arbitrary and no age ranges are reported in tables and text, above all in TOpNET group;

Reply 2: We are sorry for not elaborating why we chose 50 yrs old as the cut-off

value in the manuscript. In fact, we have considered giving look at age distribution that might more readily reveal differences- for instance less than 40 vs >60. However, we found the number of patients less than 40 was too small to conduct the research; and as indicated in the manuscript, the average age at diagnosis of pNET in China was younger than that of SEER database, obviously, >60 was not suitable for the FUSCC cohort. Therefore, we chose 50 yrs old as the cut-off value. We have added the age ranges in tables and text both in EOpNET group and TOpNET group. However, since the age distribution in SEER database is displayed into 5 years as a range, we can only also express it by an age range.

Changes in the text: We have added the age ranges in tables and text both in EOpNET group and TOpNET group.

Comment 3: -in TOpNET group proportion of elderly and very elderly patients (according to the European and International Society of Gerontology) could significantly affect results, in particular overall survival; no data are reported about this and should be added.

Reply 3: Thank you for kind reminder. We have reviewed the related literatures in Pubmed database and added the content in the discussion part.

Changes in the text: We have added the content in the discussion part.

Comment 4: - Young people are more prone to be diagnosed with functioning pNETs or Syndromic related p-NETs (i.e. MEN-1) which seem to have different biological

behaviour compared to sporadic pNETs: data about these subtypes should be reported and considered in the analysis.

Reply 4: Thanks for your suggestion. Indeed, young people are more prone to be diagnosed with functioning pNETs and syndromic related pNETs (i.e. MEN-1 or VHL) which seem to have different biological behavior compared to sporadic pNETs. All these factors may affect the results to some extent. We have reviewed the related data about these subtypes and reported and analyzed the content in the discussion part.

Changes in the text: We have reported and analyzed the content in the discussion part.

Comment 5: - in Table 1 differentiation is reported in 4 grades, while in table 2 is reported in 3 grades: which grading scale are the authors considering in Table 1?

Reply 5: Thank you for the question. In Table 1, we used the grading system in SEER database, including Well differentiated (Grade I), Moderately differentiated (Grade II), Poorly differentiated (Grade III), Undifferentiated (Grade IV).

Changes in the text: No.

Comment 6: - In FUSCC cohort, authors reported increased risk of death according to grading with important differences with SEER cohort: how do they explain such a difference?

Reply 6: Yes, though the risk of death according to grading both increased in FUSCC

cohort and SEER cohort, they have important differences. This mainly due to the grading systems were not the same. In SEER cohort, we used the grading system in SEER database, including Well differentiated (Grade I), Moderately differentiated (Grade II), Poorly differentiated (Grade III), Undifferentiated (Grade IV). While in FUSCC cohort, we used the 2010 WHO classification categorizes them into neuroendocrine tumor grade 1 (NET G1), neuroendocrine tumor grade 2 (NET G2) and neuroendocrine tumor grade 3 (NET G3) on the basis of the Ki-67 proliferation index and the mitotic count.

Changes in the text: No.

Comment 7: - Authors state that early surgical treatment should be encouraged for all pNETs patients; data about surgical resections with curative intent vs palliative/cytoreductive surgery should be reported and compared in both groups.

Reply 7: Thanks very much for your suggestion. Data about surgical resections with curative intent vs palliative/cytoreductive surgery are very important, and we have added related content in FUSCC cohort in Table 2 and the text. However, we are sorry for that we could not find the related data in SEER database.

Changes in the text: We have added related content in FUSCC cohort in Table 2 and the text.

Comment 8: - Authors reported the role of surgery on overall survival that is very important and interesting, but neither data nor informations about other treatments

(somatostatin analogues, chemotherapy, etc) are reported (no surgery for 33.1-40.5% of patients according to table 1). These data should be added and considered in analysis.

Reply 8: Thanks for your kind suggestion. We have added the related content in the analysis of discussion part.

Changes in the text: We have added the related content in the analysis of discussion part.