

Responses to the comments

ROUND 1

Dear Editor,

Your reference (63158)

Thank you very much for your e-mail dated on April 6, 2021. We are very grateful for the constructive comments given by the reviewers and you. The comments have been very helpful for us to improve our manuscript. We have carefully considered the reviewers' suggestions, and revised the manuscript. Here are the responses to each point (*the revised parts in the text have been highlighted*).

Q1: Background: The statement regarding the pathological grading adopted in the present study is placed in the background section rather than the methods section. Secondly, no mention is made about what clinical manifestations may be seen in functional as different from non-functional tumours.

Reply: Thank you so much for reminding this. First of all, we agree with the reviewer's comments, and we have placed the pathological grading standard in the method section (lines 100-111). Secondly, according to whether the tumor secretes active hormones and causes characteristic clinical manifestations, PDGNENs are divided into functional and non-functional tumors. Functional PDGNENs are extremely rare. In the introduction, we briefly introduced the clinically relevant symptoms of functional and non-functional PDGNENs (lines 67-73).

Q2: Materials and Methods: 2010 World Health Organisation classification and grading criteria was used for these tumours. A more recent edition of the World Health Organisation classification of tumours of the digestive system should be used. Also, were the tumour H&E slides reviewed to establish or confirm appropriate grading of these tumours at the time of this study in conformity with the most recent WHO classification, and, where the slides are

missing, were the paraffin embedded tissue blocks sectioned to help categorize the tumours? This is because over half of the cases had no tumour subtype documented as stated in the result section and this could be remedied by reviewing the tissue sections.

What was the role of Ki- 67 staining in this study? This was not stated throughout the manuscript.

Additionally, were all deaths due to the disease? Disease specific survival may be informative.

Lastly on this section, what treatment modalities constitute “other treatments?”

Reply: We completely agree with your suggestions.

- 1) We initially adopted the 2010 World Health Organisation classification and grading criteria, which was combined with the Chinese Gastrointestinal Pancreatic Neuroendocrine Tumor Pathological Diagnosis Consensus. **(Chinese pathologic consensus group for gastrointestinal and pancreatic neuroendocrine neoplasms. [Standardization in diagnosis of gastrointestinal and pancreatic neuroendocrine neoplasms: the Chinese consensus]. Zhonghua Bing Li Xue Za Zhi. 2013 Oct;42(10):691-4. Chinese. PMID: 24439254.)**, The 2013 China Consensus is basically the same as the 2019 WHO classification on the NEC. This article has adopted the latest 2019 World Health Organisation classification of tumours of the digestive system and reviewed all patients (lines 100-111).
- 2) Because this study is a multi-center study, it is difficult to organize the clinical data, and there will inevitably be differences between the data of each center. We also regret that half of the cases did not have tumor pathological subtype, and we have done our best to make the data more complete.
- 3) Through statistical univariate analysis of Ki-67 index, unfortunately, there is no statistical significance between Ki-67 index and prognosis. In this

study, the Ki-67 index is mainly used for the classification of PDGNENs. For GNECs, Ki-67 is greater than 20%, and its level can also guide the choice of treatment options in some cases(lines 141-144).

- 4) Through long-term follow-up, the deaths of patients are basically related to gastric malignancies. Because patients with poorly differentiated gastric neuroendocrine tumors, the prognosis is poor and the survival time is short, and their death is directly or indirectly related to the disease.
- 5) Some patients choose other treatments due to physical factors or other factors, including somatostatin analogs (SSA), targeted therapy, immunotherapy, traditional Chinese medicine treatment, etc. Since there are fewer cases of choosing other treatment methods, it has not been discussed in detail (lines 153-154).

Q3:Results: It is stated that overall 5-year survival was 5% in the section Core tips but 0% under the conclusion, these need to be reconciled.

Reply: We are sorry for this oversight. We have carefully checked and revised this in the conclusion section. We determined that the overall 5-year survival rate of PDGNENs patients in this study was 5% (line 269).

Q4: Discussion section: There is some repetition of the results in the discussion section. More needs to be done to highlight the key contributions of this study as compared with existing data.

Reply: We sincerely thank you for your excellent suggestions. After careful reading artical, I did find some repetitive content in the discussion. First of all, as to whether PDGNENs are functional or non-functional, we found that it has been discussed in the introduction and results, so we will not list it in detail in the discussion. The discussion mainly pointed out that patients with PDGNENs in the early stage, because the symptoms are not obvious, often miss the best diagnosis and treatment time. Intentionally remind people with relevant symptoms to be admitted to the hospital in time for detailed examination(lines 187-189).

Regarding the staging of PDGNENs, we have revised it during the discussion to highlight the key points. Mainly for the comparison of stage I and stage IV, the prognosis was found to be significantly different. It is still recommended to detect this disease early (lines 199-206).

For the location of PDGNENs, we found that it was mainly concentrated in the upper part of the stomach, which was shown in detail in the results, and we simplified the relevant expressions in the discussion (line 222). According to the reviewers' opinions, we focused on the key points and found that the prognosis of PDGNENs in the upper part of the stomach may be better than that in the lower part (lines 230-232).

For the treatment of PDGNENs patients, we mainly discussed the influence of the choice of treatment on the prognosis in the discussion. Especially for resectable PDGNENs, adjuvant chemotherapy can benefit patients. We recommend that patients go to the hospital in time for more adequate and correct treatment (lines 238-243).

Q5: Conclusion section: The recommendation "For patients with PDGNENs, regular endoscopy should be performed to detect lesions on the stomach, especially for patients with early-stage disease." May need to be revised since these patients are already "with PDGNEN." It needs to be observed that criteria for subject selection for "regular" diagnostic gastroscopy is not readily apparent from this study since all tumours were non-functional and only came to attention due to the mass effect of the tumour, at which time, most were at advanced stage. Is population-wide screening being advocated?

Reply: We appreciate that you pointed out the problem. This is really something that we have not explained clearly, and we are sorry for this oversight. For patients who have been diagnosed with PDGNENs, regular gastroscopy is not necessary. Electronic gastroscopy and pathological diagnosis technology have been widely used. When people have some non-specific symptoms, gastroscopy should be performed in time. If lesions

are found, pathology should be taken to make a clear diagnosis. When people perceive abnormalities, we advocate gastroscopy as the main method of screening for gastric tumors. We also recommend that people have regular physical examinations and gastroscopy to rule out the possibility of gastric tumors(lines 267-273).

Q6: References: A few of the referenced materials needs to be updated to more recent data such as that from 2005 and 2010.

Reply: We totally agree with your suggestion. We have replaced the relevant references from 2005 to 2010 with the latest references in the past three years(lines 352-359).

ROUND 2

Specific Comments To Authors: I believe that the study has met its objectives. Its importance relies on the number of studied samples and the extensive illustrations in the result section of the positive findings supporting the conclusions drawn. the title, abstract, keywords and methods are acceptable. There are few grammatical corrections required, such as this, "The data from patients treated 7 centers in China from March 2007 to November 2019 were analyzed retrospectively." Please look through for some of these and correct them.

Reply: Thank you so much for reminding this. We agree with the reviewer's comments, and we carefully checked the entire paper and adjusted the grammar of some of sentences (lines 14-15,79-80,86-87).