Yuan Qi

Editorial Board Member

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Dear Professors Qi,

We thank you and the reviewers for an excellent and thorough review of our manuscript entitled “Neuroendocrine carcinomas of the stomach: a clinicopathological, treatment, and prognosis study of 43 patients” (MS ID#: 30635). We appreciate the concerns and suggestions provided by the reviewers, and have revised our manuscript accordingly. Our point-by-point responses are sequentially provided below, and text that has been added or modified from the original text is shown in the revised manuscript and highlighted with red color. All authors of this manuscript have read and approved the final manuscript, and declared no conflict of interest.

We very much appreciate your further consideration of our manuscript and look forward to hearing from you.

Upon review of our revised manuscript, we hope that you will find it acceptable for publication in World Journal of Gastroenterology and we look forward to your response.

Sincerely yours,

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We would like to express our sincere gratitude to the reviewers for their constructive and positive comments.

Reviewer #1

Q1. The use of NET in the article is confusing. In the beginning of the Introduction, the author said: "Neuroendocrine neoplasms (NENs), which used to be called neuroendocrine tumors (NETs), are…" Here, NET is a synonym of NEN. However, in the following illustration, such as "According to this classification, GEP-NENs can be categorized as NET G1 or NET G2, or neuroendocrine carcinomas (NEC) G3." (the 3rd Paragraph of Introduction), NET is a sub-category of NEN. The authors should use the same meaning of an abbreviation throughout the manuscript.

Answer: Thank you very much for your suggestions. We are deeply sorry for the confusion. According to the new classification issued by WHO in 2010, the word "neuroendocrine neoplasms (NENs)" is a general designation which can be categorized as neuroendocrine tumors (NET) G1, or NET G2, or neuroendocrine carcinomas (NEC) G3. NET G1 or G2 are composed of tumor cells with well differentiated morphology and Ki67 ≤ 20%, while NECs have poorly differentiated histology with Ki67 > 20%. But before 2010, NETs is a general designation equivalent to NENs, so in the beginning of the introduction, we said: "Neuroendocrine neoplasms (NENs), which used to be called neuroendocrine tumors (NETs), are…" And we have made some corrections in the revised-manuscript.

Q2. Results section (P7): "…, and survival after surgery was better in patients with tumor located in the cardiac region of the stomach (median survival: 48.0 vs. 16.25/19.0/45.5 months, Car vs. Ant, P=0.0742; Car vs.Cor, P=0.0152), …" It is not clear what the numbers (16.25/19.0/45.5 months) refer to. Please state it more clearly.

Answer: Thank you for your careful review. In the revised manuscript, we have added annotations following the numbers. The numbers (16.25/19.0/45.5 months)

refer to the median survival of patients with tumor located in the gastric corpus (Cor), gastric antrum (Ant) and residual stomach anastomosis (Rsa) respectively.

Q3. As the authors stated in the Discussion, the NEC G3 category might be composed of two different entities: a group of well differentiated NETs with highly proliferation and a group of poorly differentiated NECs, including small cell carcinomas and large cell neuroendocrine carcinomas. In the present study, all the 43 patients in the present study were poorly differentiated NECs with Ki67 > 60%; among them, there are 39 small cell carcinomas and 4 large cell neuroendocrine carcinomas. Did the authors found any well differentiated NETs with highly proliferation in their cohort? If so, the clinicopathological features, treatment and prognosis of these two groups can also be compared.

Answer: Thank you for your helpful suggestions. According to the new classification issued by WHO in 2010, the main gradation standards of the NEC G3 category is that Ki67 index is >20%, so the NEC G3 category might be composed of the above two groups: a group of well differentiated NETs with highly proliferation and a group of poorly differentiated NECs. Well differentiated NETs with highly proliferation are different from poorly differentiated NECs. In our cohort of this study, all the 43 patients were poorly differentiated NECs with Ki67 > 60%. Among which, there are 39 small cell carcinomas and 4 large cell neuroendocrine carcinomas, which means that well differentiated NETs with highly proliferation were not found in our cohort.

Q4. Discussion section (P9-10): “By analysis, we found patients with tumor located in the cardiac region of the stomach (median survival: 48.0 months) survived better than those with tumor located in the gastric corpus (median survival: 16.25 months), gastric antrum (median survival: 19.0 months), and residual stomach anastomosis (median survival: 45.5 months), but there was only statistic difference between cardiac region and corpus of the stomach.” Since there was no statistic difference between cardiac and antrum, it seemed inappropriate to say that patients with tumor

located in the cardiac region of the stomach survived better than those with tumor located in the gastric antrum. Similarly, it was also inappropriate to say that patients with tumor located in the cardiac region of the stomach survived better than those with tumor located in the residual stomach anastomosis.

Answer: Thank you for your careful review. Actually, we do have an inappropriate description. We have checked and corrected this sentence in the revised manuscript, and it should be: “By analysis, we found patients with tumor located in the cardiac region of the stomach have a median survival of 48.0 months, gastric corpus 16.25 months, gastric antrum 19.0 months, and residual stomach anastomosis 45.5 months, but there was only statistic difference between cardiac region and corpus of the stomach.”

Q5. Table 1: Some contents were not easy to read, for example, T classification, Pathological stage, … Presented the data like this: “T1 0 (0%), T2 4 (9.30%), T3 0 (0%), T4 (90.70%)” is better than “T1/T2/T3/T4 0 (0%)/4 (9.30%)/0 (0%)/39 (90.70%)”.

Answer: Thank you for your helpful suggestions. We have modified it in Table 1 accordingly.

Q6. Table 2: For the parameter Lymph node metastasis, why did the authors choose 7 as cut-off value?

Answer: Thank you for your careful review. Actually, we found no statistic difference between the survival of N0 and N1. What about the effect of the number of lymph node metastasis? In the following downstream analysis, we found that lymph nodes metastasis were associated with OS of G-NEC patients, and survival after surgery was better in patients with less than 7 lymph nodes metastasis (median survival: 44.0 vs. 15.0 months, P=0.0233) than the corresponding counterparts.

Q7. In general, the paper is well written in English. However, there were some sentences and expressions definitly need to be revised. A professional editing service would be helpful.

Answer: Thank you for your suggestion. This version of the manuscript was proofread by a native English professional with a science background at Shanghai BIOMED Science Technology Co., Ltd.

Reviewer #2

Q1. In the abstract, it would be better to describe the number of patients with small or large cell carcinomas.

Answer: Thank you for your helpful suggestion. We have added it in the abstract of the revised manuscript according to your proposal.

Q2. It would be better to provide information about the patient race.

Answer: Thank you for your helpful suggestion. All the 43 patients enrolled in our study were local people of South China and we have added it in the revised manuscript.

Q3. The authors should explain how they diagnosed as neuroendocrine cancer. Did pathologists confirm the expression of neuroendocrine markers such as chromogranin A, synaptophysin, or CD56? Did the pathologists double check?

Answer: Thank you for your helpful suggestion. The diagnosis of all these 43 cases were performed according to the definition of the updated (2010) WHO classification.

Of course，other than cell morphology observed by HE staining, the expression of both chromogranin A and synaptophysin were all detected in all the specimens by immunohistochemistry (IHC). So the diagnosis of neuroendocrine cancer was double checked by pathologists through HE staining and IHC.

Q4. It would be better to explain the margin negative or not.

Answer: Thank you for your helpful suggestion. In our study, among all the 38 patients who received curative resections, the margin is negative. While the rest 5 patients with palliative resections not.

Q5. Most of the Discussion section should be summarized and moved from the Discussion section to the Introduction section, because they are about previous reports.

Answer: Thank you for your helpful suggestion. As we said in the introduction "These tumors are considered uncommon, but …..", "Epidemiological, clinical and treatment data is lack for these patients and little is got for prognostic and predictive factors." , this tumor is little known by many clinicians, even oncologists and oncological surgeons. So many previous reports about NENs were cited in the discussion to make this tumor understood fully.