Author's response to reviews

Title: Clinicopathological features and prognosis of gastroenteropancreatic neuroendocrine neoplasms in a Chinese population: a large, retrospective single-centre study

Authors:
Meng Zhang (13783554348@163.com)
Lin Zhou (ZL372@126.com)
Ping Zhao (1054601305@qq.com)
Xiaodan Shi (dandandoc@163.com)
Ahong Zhao (837110106@qq.com)
Lianfeng Zhang (ZMZZU2009@126.com)

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Author’s response to reviews:

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Clinicopathological features and prognosis of gastroenteropancreatic neuroendocrine neoplasms in a Chinese population: a large, retrospective single-centre study” (ID: BEND-D-17-00002). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewers’ comments are as flowers:

Responds to the reviewers’ comments:

Reviewer #1(Rohana Ghani):

1. Abstract: Conclusion-"Thus, early recognition and treatment is important ...." this was not reflected in the report as there was no data on delayed diagnosis.

Response: Thanks to the comments of reviewer. We have made correction according to the reviewer’s advice. In our center, the rate of distant metastases at diagnosis was high, which indicates that GEP-NENs, especially the non-functional tumors, were occult, a characteristic that could have led to delayed diagnosis and increased risk of metastasis. Moreover, our center is located in Henan Province, China, which is a relatively economically backward area. And none
of the patients underwent serum CgA testing before the lesions were found. The physicians' understanding of GEP-NENs in different hospitals is significantly different, which may lead to delayed diagnosis and treatment. At present, we are comparing the prognosis of patients who were diagnosed and treated early with those whose diagnosis and treatment were delayed. In sum, we also think the description “Thus, early recognition and treatment is important but may be difficult to achieve because the tumors are often nonfunctional and asymptomatic” is not suitable. We decide to delete it.

2. It would be interesting if the authors could attempt to explain why carcinoid was not detected in this dataset as it is the commonest NET. Response: Thanks to the comments of reviewer. The World Health Organization (WHO) classification criteria of NENs, which have been revised by an international pathological board, are basic instruments that have superseded all previous NENs classifications and terms, such as APUDoma and carcinoid. GEP-NENs were classified as neuroendocrine tumor (NET) (G1 and G2), neuroendocrine carcinoma (NEC) (G3), and mixed adenoendocrine carcinoma (MANEC) (G3). The name "carcinoid" is no longer used when GEP-NEN is diagnosed [Bosman FT, et al. WHO classification of tumours of the digestive system. 2010:1089]. In the final line on page 8 of the results section, our writing “No carcinoid tumors were present in this series” may lead to misunderstanding. Thanks to the reviewer's reminder. We have made correction as “There was no patient presented with carcinoid syndrome in our study”. We consider the reviewer mean “why carcinoid syndrome was not detected in this dataset”. Carcinoid syndrome was not detected in this dataset, and the finding was similar to a low reported frequency of these tumors in Asian. The other two studies in China included 178 patients and 122 samples, both of which did not find patients with carcinoid syndrome [Wang Y-h, et al. BMC Endocrine Disorders, 2012, 12; Zeng YJ, et al. Asian Pacific Journal of Cancer Prevention, 2013, 14]. However, the incidence of carcinoid syndrome (11.5% to 31.1%) in the Western population is relatively high [Pape UF, et al. PubMed, 2004; Pape UF, et al. Endocrine Related Cancer, 2008, 15; Ploeckinger U, et al. Neuroendocrinology, 2009, 90]. Carcinoid syndrome occurs mainly in the neuroendocrine neoplasms of jejunum/ileum. In the western population, the proportion of neuroendocrine neoplasms of jejunum/ileum is high, which is only 1.8% in our study. (Discussion section, line 2-6, page 13)

3. Line 53- 'The distribution of GEP-NENs in our population was similar to....and other Chinese population." Reference 4 seems to be from the same institution thus would explain the similarity.

Response: Thanks to the question of reviewer. Reference 4 is a research of the First Affiliated Hospital of Sun Yat-sen University, which is located in the south of China. Our date is from the First Affiliated Hospital of Zhengzhou University located in the north of China which is about one thousand kilometers away from the First Affiliated Hospital of Sun Yat-sen University. As the largest ethnic group in China, Han ethnic group makes up 92 percent of the total population. The patients of the two hospitals mentioned above are totally Han people. The similar ethnic may lead to similarity in the reported distribution of the primary sites of GEP-NENs about the two institutions. China is building a nationwide cancer registration system now. And the differences in clinicopathological features and prognosis of GEP-NENs among the ethnics will be completed in the near future. Thanks to the reviewer for your good advice.
4. Conclusion: "It is our hope ..., GEP-NENs will improve physicians' knowledge of the tumors and result in earlier recognition..." similarly, this was not reflected in the result. Distant metastases were found in 20.5% of patients. The authors commented that "Limited financial resources... infrequent use of newer and experimental therapies..." Perhaps this could be a more probable explanation on poorer prognosis compared to Western data.

Response: It is really true of reviewer’s suggestion. We have re-written this part according to the reviewer’s suggestion. For there was no date on delayed diagnosis currently, the description “It is our hope that this extensive analysis of GEP-NENs will improve physicians’ knowledge of the tumors and result in earlier recognition and possibly improved prognosis for Chinese patients.” was not suitable. We decide to delete it. Biological and targeted therapies show great promises against NENs. Somatostatin can reduce the symptoms of excessive secretion of hormones and play the role of antitumor [Toumpanakis C, et al. Seminars in Oncology, 2013, 40]. Two targeted agents, sunitinib and everolimus, have demonstrated antiproliferative effect in inoperable locally and advanced or metastatic, progressive p-NET [Raymond E, et al. New England Journal of Medicine, 2011, 364; Yao JC, et al. New England Journal of Medicine, 2011, 364]. Only 6 patients were treated with biological therapy and none with targeted therapy. Our center is located in Henan Province, China, which is a relatively economically backward area. The treatment of GEP-NENs was decided largely by the economic levels of different regions. Thanks to the advice of reviewer. We have re-written it as follows: And limited financial resources in our area may lead to the infrequent use of newer or experimental therapies for GEP-NENs. Perhaps this could be a probable explanation on poorer prognosis compared to Western data. (Conclusion section: line 1-4, page 18).

Special thanks to you for your good comments.

Reviewer #2 (Lefteris Chatzellis, MD):

1.p.8 paragraph "Imaging studies": The statistics of each imaging modality's success in detecting NENs are somewhat misleading. For example PET is 93% positive but in 29 cases only probably the g3 tumors. Moreover, the choice of each modality depends on the site of origin and tumor histopathology i.e. PET/CT is indicated in g3 tumors but not g1, endoscopy is the examination of choice for rectal or gastric NENs but not for small intestinal or lung NENs. This paragraph should be rewritten and rephrased.

Response: Thanks very much to the advice of reviewer. We have made correction according to the reviewer’s comments: All imaging examinations can be found in any grade of tumors. Endoscopy, endoscopic ultrasound (EUS) and positron emission computed tomography imaging (PET-CT, using with 18F-FDG) were positive in >90% of cases. Magnetic resonance imaging (MRI) was the least often positive (79.5%). But MRI and PET-CT, were performed in only about 10% of patients, respectively. MRI is mainly used for the detection of pancreatic and liver's tumors and PET-CT for tumors in any part of the digestive system. EUS was performed on 41 patients, of which a lesion was found in 38 patients. At endoscopy, which is used for the detection of gastrointestinal tract tumors, the GEP-NENs usually appeared as ulcers or polypoid prominences. And the results of imaging examinations are summarized in Table 1. Thus, for
tumors in different sites, the choice of appropriate examination is very important. Thanks to the advice of reviewer again. (Result: Imaging studies section, line 1-2 and 5-9, page 8)

2.p.8 "PET-CT revealed increased metabolites" does not read well - needs rephrasing.

Response: We are very sorry for our unsuitable expressing of "PET-CT revealed increased metabolites". We have rephrased it as follows: PET-CT usually revealed high glucose metabolism in GEP-NENs, especially in poorly differentiated NENs. (Result: Imaging studies section, line 14-15, page 8)

3.p12 "Ethnic, regional and sample-size differences may lead to differences in the reported distribution of the primary sites of GEP-NENs" I am not sure whether ethnic and sample-size differences are the only possible explanation for the differences mentioned. It seems there could be referral bias in the reported series (patients referred to Gastroenterology department) and thus comparison with epidemiological data from SEER and other national databases is not valid.)

Response: Thanks to the reviewer for your good advice. Our data are collected from our center’s case database. Most of the patients were admitted to the Department of Gastroenterology and Department of Oncology. During the treatment, the patients were transferred to the Hepatopancreatobiliary Surgery, Gastrointestinal Surgery, or Interventional Department for surgical treatment if it is needed. Patients, without surgical indications, received medical treatment in the Department of Gastroenterology and Department of Oncology. A small number of patients were admitted to the Department of Respiratory Medicine, Department of Endocrinology or Department of Neurology and so on. The distribution of GEP-NENs in our population was similar to that found in other Chinese populations [Wang Y-h, et al. BMC Endocrine Disorders, 2012, 12; Zeng YJ, et al. Asian Pacific Journal of Cancer Prevention, 2013, 14; Jiao X, et al. Chinese Journal of Cancer Research, 2015, 27]. In recent years, China's GEP-NENs reports also gradually increased. But the nationwide tumor registration system has not been established yet at present, so the epidemic trends, clinical features and prevention of GEP-NENs in China are not clear now, lacking of comparable data with other countries. China is building a nationwide tumor registration system now. Thus, comparison with epidemiological data from SEER and other national databases will be more valid in the near future. Thanks to the reviewer for your good advice again.

4.Lack of somatostatin receptor scintigraphy data is a relative weak point of the study.

Response: We are sorry for the lack of somatostatin receptor scintigraphy data. Somatostatin receptor scintigraphy is considered a comprehensive imaging modality for many neuroendocrine tumors. In a meta-analysis, GaTate PET-CT demonstrated a sensitivity of 93% and a specificity of 95% [Geijer H, et al. European Journal of Nuclear Medicine and Molecular Imaging, 2013, 40]. GaTate PET-CT should be considered the first-line diagnostic imaging modality of choice for tumors with high Somatostatin receptors (SSTR) expression. In addition, GaTate PET-CT and FDG PET-CT are complementary and help identify both well- and poorly differentiated phenotypes [Hofman MS, et al. Radiographics, 2015, 35]. But unfortunately, our institution had not this methodology for the past years. Since January 2017, Somatostatin receptor scintigraphy examination has already been applied in our center. This method of examination greatly
improves the detection rate of the tumor. As more and more patients receive this examination, we will collect and analyze the data in the future studies. Thanks to the comments of reviewer again.

5. Liver NENs and biliary tree NENs are reported to be extremely rare (<1%), however their incidence in the present study is surprisingly higher (4.3% and 3.6%). Presence of primary hepatic NENs is very difficult to be distinguished from metastatic NENs arising from other organs (requires exclusion of other primaries with imaging, scintigraphy and/or immunohistochemical markers). Maybe the term UPO-NEN (unknown primary origin) is more appropriate if diagnostic evaluation is not complete.

Response: It is really true as reviewer suggested that UPO-NEN (unknown primary origin) is more appropriate. The diagnostic criterias of Liver NENs or biliary tree NENs in our study are as follows: ① postoperative or biopsy pathological diagnosis of Liver NENs or biliary tree NENs; ② exclude the tumors of other parts; ③ excluding primary liver cancer, mixed liver cancer, hilar cholangiocarcinoma and extrahepatic cholangiocarcinoma; ④ complete clinical data; ⑤ during clinical follow-up period, the primary lesions besides the liver were not found. However, it is our pity that some of the inspection methods are not available in our center such as somatostatin receptor scintigraphy and some patients’ diagnostic evaluation is not complete like PET-CT. And the follow-up time is relatively short. During the follow-up period, the primary sites were finally diagnosed as lung (13 cases) and adrenal gland (3 cases), while they were identified as liver initially. And such cases were excluded from our study. There are 7 cases whose primary sites were finally diagnosed as the pancreas during the visit, having been classified as pancreatic NENs. So presently, whether these tumors come from other parts of the digestive system is not clear yet. According to the recommendation of the reviewer, we also think change them as UPO-NENs (unknown primary origin) more appropriately. We will continue to focus on the follow-up of these cases. Thanks to the precious advice of reviewer.

(Abstract: Result section, line 12, page 2; Result: Clinical features section, line 4, page 7)

GENERAL COMMENT: Overall this paper reports the experience of a single-center institution in neuroendocrine tumors. Whether the findings represent the true figures for the entire Chinese or regional population is unclear. Several statistics reported such as incidence of each NEN, metastatic disease at diagnosis, percentage of functioning tumors etc, vary significantly from those in the European and north-American literature. Considering author affiliations (mostly from Department of Gastroenterology) referral bias could have played a role in the aforementioned differences.

Response: Thanks to you for your good comments very much. Our findings represent the figures for the regional population in China. The patients in our study mainly come from Henan Province, China, which is a relatively economically backward area. The physicians' understanding of GEP-NENs in different hospitals is significantly different, which may lead to delayed diagnosis and treatment. China is building a nationwide cancer registration system now. Thus comparison with epidemiological data from SEER and other national databases will be more valid in the near future. Thanks to the reviewer for your good advice again.
We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we list the changes and marked in red in revised paper.

We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.