Author's response to reviews

Title: Relationship between clinical characteristics and survival of gastroenteropancreatic neuroendocrine neoplasms: A single-institution analysis (1995 - 2012) in South China

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Author's response to reviews: see over
Oct. 20, 2012

Dear Editor,

I am submitting a revised manuscript entitled “Relationship between clinical characteristics and survival of gastroenteropancreatic neuroendocrine neoplasms: A single-institution analysis (1995 – 2012) in South China (MS ID: 2065958399782727)” for considering publication in BMC Endocrine Disorders.

The paper has been revised in accordance with comments and suggestions made by the reviewers. Modifications are highlighted by underscoring the revised text and are listed on the following page.

Should there be any further comments on the manuscript, please do not hesitate to contact me.

Thank you for considering our paper for publication in your Journal.

Yours sincerely,

[Signature]

Prof. Dr. J Chen (Ph. D)                     Prof. Dr. M.H. Chen (M.D., Ph. D)
Revision made in the manuscript

Editorial comments:

1. Please remove the reference to Steve Jobs in your opening paragraph as this does not bear scientific relevance to the content of your manuscript.

Responses:

We agree the opinion of the editor. We remove the reference to Steve Jobs in the first paragraph and add statement in our manuscript as following:

Page 4, line 2

Added: “Neuroendocrine neoplasms, which originate from neuroendocrine cells distributed throughout the body, comprise a heterogeneous family with a wide and complex spectrum of clinical behaviors [1]”

2. Experimental research that is reported in the manuscript must have been performed with the approval of an appropriate ethics committee. Research carried out on humans must be in compliance with the Helsinki Declaration (http://www.wma.net/e/policy/b3.htm), and any experimental research on animals must follow internationally recognized guidelines. A statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate.

Responses:

We do agree the opinion of the editor. According to the editor’s suggestion, we add this comment in the Methods section of the manuscript.

Page 5, line 28

Added: “The study was approved by the ethics committee of The First Affiliated Hospital Sun Yat-sen University (with a reference number: [2012]317) and complied with the Declaration of Helsinki.”

3. Further consideration of your manuscript is conditional on improvement of the English used - please bear in mind that as we are a free-access publisher, we cannot
bear the costs of copyediting English ourselves. Please ensure particular attention is paid to the abstract. You should have a native English speaking colleague help you with this, if possible, or you may need to use a professional language editing service. For authors who wish to have the language in their manuscript edited by a native-English speaker with scientific expertise, BioMed Central recommends Edanz (www.edanzediting.com/bmc1). BioMed Central has negotiated a 10% discount to the fee charged to BioMed Central authors by Edanz. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication. For more information, see our FAQ on language editing services at http://www.biomedcentral.com/info/authors/authorfaqs#12.

**Responses:**
According to the editor’s suggestion, the manuscript has been reviewed by an English editor and all the grammar mistakes have been corrected.
Reviewer: Anja Rinke

Reviewer's report:

1. Although - as mentioned several times - the analysis is done according to the new WHO classification and there are limited data regarding NEN in China, it should be clearly stated that it is just a retrospective analysis of one hospital. The comparisons made in the discussion includes population based data (like SEER) and hospital series which of cause are not comparable because of selection bias.

Responses:

We totally agree with the reviewer on this point. SEER, RGETNE and NRC which were referred in the discussion are all population based data. The study we did wasn’t population based data and was just a retrospective analysis of one hospital. However, due to the rarity of this heterogeneous tumor, not complete database from China exists. This preliminary data we provided was from the largest comprehensive medical center in South China. During the process of collecting patients’ data, we have tried to avoid selection bias. Besides, there were several prior single-center studies in other countries also compared with population based data (like SEER) in their reports (see reference: Pape UF and Bohmig M, 2004; Li AF and Hsu CY, 2007; Ozcan Yildiz and Mustafa Ozguroglu, 2010; Su-Jung Kim and Jin Won Kim, 2011; Lim T and Lee J, 2011). So we prefer to keep the comparisons in our manuscript. Further investigation in a larger patient population is required to estimate the prevalence and clinical pathological characteristics of GEP-NENs in the general population. According to the reviewer’s suggestion, we modify the discussion part of the manuscript.

Page 10, line 28

Modified from: “These inconsistencies may be due to the racial disparities as well as the influence of patient selection among different data bases.”

To: “These inconsistencies may be due to the racial disparities, as well as the selection bias among population based data and hospital series. So a larger patient population is required to carry on further investigation.”
2. It should be discussed that functionality may be a favorable prognostic marker in this series as the great majority of functioning tumors were insulinomas which are benign in most cases.

**Responses:**

We totally agree with the reviewer. The result obtained above may be caused by small sample in this series. We are preparing to perform a multicenter study and collect much more patients’ data so that we can achieve an exact result on the relation of functionality and survival. According to the reviewer's suggestion, we also add this comment in the discussion part of the manuscript.

**Page 14, line 5**

**Added:** “As the great majority of functional tumors were insulinomas which are benign in most cases in our study, that may lead to the conclusion that functionality may be a favorable prognostic marker. The result obtained above may be caused by small sample in this series.”

Please also see my comments on the paper.

**Responses:**

We agree the comments of the reviewer on the paper. We give a point-by-point response to the concerns as following:

a) **Page 3, line 14**

**Modified from:** “Positive rates of chromogranin A (CgA) and synaptophysin (Syn) were 69.1% and 90.2% respectively.”

**To:** “Positive rates of chromogranin A (CgA) and synaptophysin (Syn) were immunohistochemically 69.1% and 90.2% respectively.”

b) **Page 3, line 15**

**Modified from:** “87 (51.5%) patients were at G1 phase, 31 (18.3%) at G2, and 51 (30.2%) at G3.”

**To:** “87 patients (51.5%) had G1 tumors, 31(18.3%) G2 tumors and 51 (30.2%) G3 tumors.”
c) **Page 3, line 20**

**Modified from:** “Functional tumors, patients were at G1 phase and classified as NET were superior to other types of NENs in survival by univariate analysis. Distant metastasis also contributed to the prognosis of these tumors.”

**To:** “Functionality, G1 grading and classification as NET (versus NEC/MANEC) were associated with favorable prognosis in univariate analysis. Distant metastasis contributed to unfavorable prognosis of these tumors.”

d) **Page 4, line 4**

**Modified from:** “A 5-decade analysis of 13,715 carcinoid tumors demonstrated that the incidence of NENs range from 2.5 to 5 cases per 100,000 in the United States, and the gastrointestinal tract (67.5%) is the most commonly affected site [2].”

**To:** “The incidence of NENs ranges from 2.5 to 5 cases per 100,000 in the United States, and the gastrointestinal tract is the most commonly affected site [2, 3].”

e) **Page 5, line 21**

**Modified from:** “GEP-NENs were classified as NET (G1 and G2 phases), NEC (G3 phase) and MANEC (G3 phase)”

**To:** “GEP-NENs were classified as NET (G1 and G2), NEC (G3) and MANEC (G3)”

f) **Page 10, line 28**

**Modified from:** “These inconsistencies may be due to the racial disparities as well as the influence of patient selection among different data bases.”

**To:** “These inconsistencies may be due to the racial disparities, as well as the selection bias among population based data and hospital series. So a larger patient population is required to carry on further investigation.”

g) **Page 13, line 3**

**Modified from:** “adjuvant therapeutic options such as chemotherapy”
To: “other therapeutic options such as chemotherapy”

h) Page 13, line 4

**Modified from:** “Patients with GEP-NEC and GEP-MANEC are generally applied with cytotoxic chemotherapy agents, which are considered ineffective for GEP-NETs.”

**To:** “According to the new WHO 2010 classification, well-differentiated NENs are classified as G1 and G2 neuroendocrine tumors (NETs) and poor-differentiated NENs are referred to as G3 neuroendocrine carcinomas (NECs). It has been reported that existing cytotoxic chemotherapy agents have been of limited value for the treatment of well-differentiated gastrointestinal NENs (with response rates 10%~15%) [27-29], but has been the standard of care for well-differentiated metastatic pancreatic endocrine tumors (with response rates 40%~70%) [30-32]. However, chemotherapy is generally considered active in poor-differentiated NENs (with response rates 50%~70%) [33-35].”

Page 13, line 20

**Modified from:** “It has been demonstrated that somatostatin analogs are effective not only in controlling hormone overproduction but also in tumors shrinkage [39].”

**To:** “Somatostatin analogues are effective therapeutic option for functional neuroendocrine tumors because they reduce hormone-related symptoms [44-46]. They have also been shown to stabilize tumor growth over long periods, even to inhibit tumor growth in patients with well-differentiated metastatic neuroendocrine midgut tumors [40,47,48].”

Quality of written English: Needs some language corrections before being Published

**Responses:**
According to the editor’s suggestion, the manuscript has been reviewed by an English editor and all the grammar mistakes have been corrected.
Reviewer: Frederico Costa

Reviewer's report:

Major Compulsory Revisions

On page 4: I recommend changing the first paragraph “On October 5, 2011, Steve Jobs Godfather died at his California home, due to respiratory arrest, a severe complication resulted from relapse of his previously treated pancreatic neuroendocrine carcinoma. The death of Jobs aroused widespread concern about a particular kind of tumors—neuroendocrine neoplasms, which originate from neuroendocrine cells distributed throughout the body, and comprise a heterogeneous family with a wide and complex spectrum of clinical behaviors”. The statement is not scientific and does not add meaningful information.

Responses:
We agree with the reviewer. According to the opinion of the reviewer, we remove the reference to Steve Jobs in the first paragraph and add statement in our manuscript as following:

Page 4, line 2

Added: “Neuroendocrine neoplasms, which originate from neuroendocrine cells distributed throughout the body, comprise a heterogeneous family with a wide and complex spectrum of clinical behaviors [1]”

On page 12:

a) “Besides surgery, adjuvant therapeutic options such as chemotherapy, biological therapy and targeted therapy can be used for NENs.” This statement is not supported by the current available literature. If the authors are convinced that this statement is real, they should support with convincing references.

Responses:
We do agree on the opinion of the reviewer. Adjuvant therapy is a cancer treatment (chemotherapy, radiation, or biological therapy) that is offered after a surgical procedure in order to improve the outcome of patients at high risk of relapse. There
are not any current available literatures to support the view that NENs need adjuvant therapeutic options. The statement in our original manuscript was improper.

Page 13, line 3

**Modified from:** “adjuvant therapeutic options such as chemotherapy”

**To:** “other therapeutic options such as chemotherapy”

b) “Patients with GEP-NEC and GEP-MANEC are generally applied with cytotoxic chemotherapy agents, which are considered ineffective for GEP-NETs.” I believe the authors are referring to differences in response to chemotherapy agents according to low vs high grade tumors. Unfortunately the statement is not clear. This statement needs clarification and more supporting references.

**Responses:**

We agree the opinion of the reviewer. GEP-NENs classified as G1 and G2 are Well-differentiated neuroendocrine tumors (NETs) according to the WHO 2010 classification. However, high grade (G3) neuroendocrine carcinomas (NECs) are poorly differentiated tumors that are aggressive and rapidly growing. It has been reported that responses to chemotherapy agents according to low vs high grade tumors are different. To make article more clearly, we modified our manuscript as following:

Page 13, line 4

**Modified from:** “Patients with GEP-NEC and GEP-MANEC are generally applied with cytotoxic chemotherapy agents, which are considered ineffective for GEP-NETs.”

**To:** “According to the new WHO 2010 classification, well-differentiated NENs are classified as G1 and G2 neuroendocrine tumors (NETs) and poor-differentiated NENs are referred to as G3 neuroendocrine carcinomas (NECs). It has been reported that existing cytotoxic chemotherapy agents have been of limited value for the treatment of well-differentiated gastrointestinal NENs (with response rates 10%~15%) [27-29], but has been the standard of care for well-differentiated metastatic pancreatic endocrine tumors (with response rates 40%~70%) [30-32]. However, chemotherapy is
generally considered active in poor-differentiated NENs (with response rates 50%~70%) [33-35].”

c) “In our cohort, chemotherapy was performed in 23 patients, 3 of them died during follow-up. The most frequently used agents were platinum salts.” The statement is very vague. I recommend better data clarification and details regarding the treatment regimens most used in China. Is the patients’ death related to treatment or disease progression?

**Responses:**
Etoposide–platinum combination is an effective regimen for G3 NECs, with major anti-tumoural activity and high tumour response rates (41~67%) reported in the main series published in the previous studies. (see references: Mitry E and Baudin E, 1999; Fjallskog ML and Granberg DP, 2001; Nilsson O and Van Cutsem E, 2006; Ahlman H and Nilsson O, 2008.). The chemo regimen is also the most commonly used treatment option in China. We do agree the opinion of the reviewer that “the statement is very vague”, thus we modified our manuscript as following:

**Page 13, line 16**

**Modified from:** “In our cohort, chemotherapy was performed in 23 patients, 3 of them died during follow-up. The most frequently used agents were platinum salts.”

**To:** “In our cohort, chemotherapy was performed in 23 patients. The most frequently used chemo regimen was etoposide–platinum combination. During follow-up, 3 of them died of tumor progression.”

d) “In this study octreotide LAR was given to 16 patients at a dose of 20-40 mg monthly.” If carcinoid syndrome was not observed in this cohort and functional tumors correspond to a small fraction of patients, the authors should describe the indication for somatostatin analogs in China.

**Responses:**
Previous studies revealed that somatostatin analogues were the best therapeutic option for functional neuroendocrine tumors because they reduce hormone-related symptoms.
However, somatostatin analogues have also been shown to slow tumor growth in some clinical studies (see references: Faiss S and Rath U, 1999; Welin SV and Janson ET, 2004). The PROMID phase 3 study (see references: Rinke A and Muller HH, 2009) showed that long-term administration of octreotide LAR inhibited tumor growth and more than doubled the time to tumor progression in patients with well-differentiated metastatic neuroendocrine midgut tumors (14.3 months) compared with placebo (6 months). Although the treatment effect of somatostatin analogues on foregut and hindgut tumors remain to be confirmed, many large general hospitals use somatostatin analogues to cure patients with well-differentiated metastatic tumors not only in midgut but also in foregut and hindgut in China. That is the reason that 16 patients including 2 patients with functional neuroendocrine tumors and 14 patients with well-differentiated metastatic GEP-NENs received long-term administration of octreotide LAR in our study. In order to make the statement more reasonable, we modified our manuscript as following:

**Page 13, line 20**

**Modified from:** “It has been demonstrated that somatostatin analogs are effective not only in controlling hormone overproduction but also in tumors shrinkage [39]. In this study octreotide LAR was given to 16 patients at a dose of 20-40 mg monthly.”

**To:** “Somatostatin analogues are effective therapeutic option for functional neuroendocrine tumors because they reduce hormone-related symptoms [44-46]. They have also been shown to stabilize tumor growth over long periods, even to inhibit tumor growth in patients with well-differentiated metastatic neuroendocrine midgut tumors [40,47,48]. Although the treatment effect of somatostatin analogues on foregut and hindgut tumors remain to be confirmed, 16 patients including 2 patients with functional neuroendocrine tumors and 14 patients with well-differentiated metastatic GEP-NENs received long-term administration of octreotide LAR at a dose of 20-40 mg monthly in our study.”

e) “We also proved that prognosis differed significantly according to functional status, pathological grading and classification. We also confirmed that metastasis represented
a worse outcome with a mean survival of 5.0 years (P=0.000). Multivariate analysis was not done due to the small size of our series.” The data presented in this manuscript does not support this conclusion. If the authors are referring to different data set, they should add the reference.

Responses:

Univariate analysis showed that tumor functional status, pathological grading, classification and condition of metastasis seemed correlate to the prognosis of patients (see table 4 and figure 1). Further multivariate analysis was not done in our study due to the small size of our series. However, the more convincing factors associated with the prognosis of GEP-NENs should be verified by a much larger sample size.

Page 14, line 4

Modified from: “that prognosis differed significantly according to functional status.”

To: “that prognosis differed statistically according to functional status.”

- Minor Essential Revisions

On page 5:

a) second paragraph “Tumors with a Ki-67 index of < 2% were classified as G1 tumors”, change to # 2

b) “GEP-NENs were classified as NET (G1 and G2 phases), NEC (G3 phase) and MANEC (G3 phase)”. Please, remove phase(s)

Responses:

According to the reviewer’s suggestion, we modified our manuscript as following:

a) Page 5, line 16

Modified from: “Tumors with a Ki-67 index of <2% were classified as G1 tumors”

To: “Tumors with a Ki-67 index of < 2% were classified as G1 tumors”

b) Page 5, line 21

Modified from: “GEP-NENs were classified as NET (G1 and G2 phases), NEC (G3 phase) and MANEC (G3 phase)”

To: “GEP-NENs were classified as NET (G1 and G2), NEC (G3) and MANEC (G3)”
On page 6:
a) “The most common sites was the pancreas, comprising 34.8%(62/178) of tumor invasion”. The phase is not clear. Please re-phrase it.
b) “Other sites included appendix, jejunum/ileum, Vater's ampulla, etc. at 12.9% (23/178)”. Please, remove etc.
c) “Local compression was rather common in nonfunctional tumors, giving rise to a variety of gastrointestinal manifestations.” I don’t understand what the authors mean with local compression.

**Responses:**
According to the reviewer’s suggestion, we modified our manuscript as following:

a) **Page 7, line 5**
Modified from: “The most common sites was the pancreas, comprising 34.8% (62/178) of tumor invasion”
To: “The most common sites was the pancreas (62/178, 34.8%)”

b) **Page 7, line 8**
Modified from: “Other sites included appendix, jejunum/ileum, Vater's ampulla, etc. at 12.9% (23/178)”
To: “Other sites included appendix, jejunum/ileum, Vater's ampulla at 12.9% (23/178)”

c) The phrase “local compression” in the sentence means tumors compress nearby organs and healthy tissue give rise to a variety of gastrointestinal manifestations. To make the statement more clearly, we modified it as following:

**Page 7, line 10**
Modified from: “Local compression was rather common in nonfunctional tumors, giving rise to a variety of gastrointestinal manifestations.”
To: “A variety of gastrointestinal manifestations were caused by the effect of local compression on nearby tissues in nonfunctional tumors.”

On page 7: “Over half (51.5%) of the tumors were at G1 phase.” Please, change to “were G1”.
Responses:
According to the reviewer’s suggestion, we modified our manuscript as following:

Page 8, line 13

Modified from: “Over half (51.5%) of the tumors were at G1 phase.”
To: “Over half (51.5%) of the tumors were G1.”

Quality of written English: Not suitable for publication unless extensively edited

Responses:
According to the editor’s suggestion, the manuscript has been reviewed by an English editor and all the grammar mistakes have been corrected.
Reviewer: CHRISTOS TOUMPANAKIS

Reviewer's report:

Major Compulsory Revisions

1. Have the Authors screened the patients for MEN-1 syndrome? If yes, what was the incidence of MEN-1 in their patients' population?

Responses:
During the process of collecting the patients’ medical records, we had tried to screen the patients for MEN-1 syndrome. Unfortunately, there was only 1 case collected in the past 17 years. Thus we decided to exclude MEN-1 syndrome when analyzed the data. We are so sorry that we can’t provide the incidence of MEN-1 in their patients' population. In order to make the readers clearer, we add this comment in the manuscript.

Page 5, line 2
Added: “178 patients with histologically confirmed and sporadic GEP-NENs”

2. What was the response of non-surgical therapies that the patients had? Did those responses have any impacts on survival?

Responses:
26 patients received non-surgical therapies in our study. 14 cases out of them were treated only with supportive care because of progressive malignant disease. Among 14 patients, only 3 out of them were still alive at the last follow-up, 5 cases died of tumor progression and 6 lost to follow-up. The rest of 12 cases were treated with different kinds of therapies which consisted of chemotherapy (4/12), biological therapy (3/12), hepatic regional therapy (1/12) and combination (4/12). Among 12 patients, 4 cases died of tumor progression and 8 were still alive during the follow-up.

Since a small number of patients received non-surgical therapies which consisted of different kinds of therapies, we didn’t analyze the impacts of those responses on survival. According to the reviewer’s meaningful suggestion, we plan to collect much
more patients’ data in our ongoing study, so that we can analyze impacts on survival according to different responses to different kinds of therapies.

3. The Authors stated that distant metastases also contributed to the prognosis. Do they mean distant metastases at presentation or during the course of the disease?

**Responses:**
In our study, we analyzed distant metastases both at presentation and during the course of the disease. There were 36 out of 136 patients who received long-term follow up manifested distant metastasis at diagnosis, another 8 patients developed distant metastases during the course of the disease. 44 patients with distant metastases in all were included in the univariate analysis.

4. Did hepatic tumour load have any impact on survival?

**Responses:**
In our study, liver metastasis occurred in 44 patients during the past 17 years. We couldn’t obtain the data of hepatic tumor load in most of patients because of a long time span. There weren’t enough imaging data to evaluate patients’ hepatic tumor load, so we didn’t analyze the impact of hepatic tumor load on survival. Furthermore, there are only a few studies analyzing the relation between hepatic tumor load and survival (for example, the PROMID study).

Minor essential revisions

1. As Somatostatin Receptor Scintigraphy is almost mandatory in the initial work-up of patients with advanced NENs, the Authors need to explain why this was not performed in any of their patients.

**Responses:**
We do agree the opinion of the reviewer. Unfortunately, a large number of hospitals in China haven’t carried out somatostatin receptor scintigraphy yet. This examination was performed in our hospital only in the latest year.
2. The Authors need to clarify which isotope was used in PET scan. Was it 16F-FDG?

**Responses:**
We totally agree the opinion of the reviewer. The isotope used in PET scan is 16F-FDG in our study. According to the reviewer’s suggestion, we add the comment in our manuscript.

**Page 7, line 27**

**Added:** “and positron emission computed tomography imaging (PET-CT, using with 16F-FDG)”

3. I would suggest that the term "G phase" need to be replaced with G grade.

**Responses:**
We totally agree the opinion of the reviewer. According to the reviewer’s and the other reviewer’s suggestion, we removed “phase(s)” in our manuscript.

Quality of written English: Not suitable for publication unless extensively edited

**Responses:**
According to the editor’s suggestion, the manuscript has been reviewed by an English editor and all the grammar mistakes have been corrected.