ANSWERS TO REVIEWERS

12 June, 2014

Dear Editor Gou

Please find enclosed our new revised manuscript in Word format (file name: 10590_Revised Manuscript, Clean version_12 June 2014.doc).

Title: Characteristics and long-term prognosis of patients with rectal neuroendocrine tumors

Authors: Yihebali Chi, Feng Du, Hong Zhao, Jinwan Wang, Jianqiang Cai

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 10590

Thank you very much for your comments and suggestions. The manuscript has been improved according to the suggestions of the reviewers and the editor's comments in the manuscript that was returned to us.

A new 'clean' revised manuscript (dated 12 June 2014) is herewith submitted to *World Journal of Gastroenterology*, which we trust will be acceptable for publication in the journal. As part of our revision, the format of the manuscript has been amended and, where necessary, updated.

Note: As well as the new 'clean' version of the revised manuscript (dated 12 June 2014), a version showing the new changes in red type is also attached. The changes shown in this version are additional to those in the 'Tracked changes' version previously resubmitted. In the new 'clean' version dated 12 June 20124, the text is in normal type font but is otherwise

identical to the 'New changes in red' version.

Responses to the Reviewers and Editor

Firstly, we would like to thank both the reviewers and editor for their positive and constructive comments and suggestions.

RESPONSES TO REVIEWER #1:

1) In your cases, you have the pathologic reports and staging only in 52 cases among 57 total cases. Would you analyze 52 cases? I think the incompletely evaluated cases should be discard.

Response: **We accept your constructive suggestion. We have re-examined our database and deleted 9 cases who did not have complete medical records. Thus, 48 cases with sufficient clinical data and follow-up time are included in the new revised version of manuscript. Their clinicopathologic characteristics were analyzed and the prognostic value of various factors was assessed.**

2) You used the European Neuroendocrine Tumor Association (ENETS) in 2007 for tumor staging. Please describe this staging system for understanding.

Response: **We accept the reviewer's comment. In the new revised version of the manuscript, we have added information on the ENETS 2007 staging of rectal neuroendocrine tumors in the manuscript (see Tables 1 and 2). All patients described in the manuscript were staged according to the ENETS 2007 staging criteria.**

RESPONSES TO REVIEWER #2:

1) The authors should use ENETS/ AJCC staging system.

Response: **Thank you for your comment. We used the TNM staging system of the European Neuroendocrine Tumor Society (ENETS) which was updated in 2007. Information on the ENETS 2007 staging system has added in Tables 1 and 2 of the new revised manuscript.**

2) Data on mitotic rate and Ki 67 index as well as lymphovascular invasion are missing.

Response: **We agree that the mitotic rate, Ki-67 index, and lymphovascular invasion are important prognostic factors for neuroendocrine tumors. However, all the patients included in our study were diagnosed between 2004 and 2009 when specific IHC staining for these factors was not conducted. Therefore, we were not able to analyze the prognostic value of these factors in our study.**

3) In the results and discussion parts of the manuscript comparison in five year survival among different age groups should be done according to the same tumor type and stage groups.

Response: **We accept the reviewer's comment. We have added an analysis stratified by tumor type and TNM stage comparing 5-year survival rates in the different age groups. Subgroup analysis showed that the 5-year survival rate in patients aged ≥55 years was lower than in those aged <55 years when they had atypical rectal neuroendocrine tumors or disease at TNM stage III/IV. However, the 5-year survival rates were very close in patients with typical neuroendocrine tumors or TNM stage I/II regardless of age, which suggests that the tumor type and TNM stage contribute greatly to a poorer prognosis in older patients. The results are summarized in a new table (Table 3) in the revised manuscript.**

Note: **The new tables for the manuscript (Tables 1-3) are also provided as a separate file.**

4) The exact data are not clarified. All possible therapeutic approaches are not mentioned in the text: when can only EMR or ESD be performed; which diagnostic tests are necessary before therapeutic decision.

Response: **Thank you for your comment. We agree that some more information about the diagnostic tests and treatments needs to be provided. It is well accepted that colonoscopy and pathological data are the "gold standard" for establishing the diagnosis of rectal neuroendocrine tumors. All patients in our study underwent colonoscopy and the diagnosis was confirmed by pathological findings. Furthermore, some other diagnostic test such as a CT scan and ultrasound endoscopy were also helpful in choosing the appropriate treatment. Therefore, we supplemented the data to describe the proportions of patients who received a CT scan or ultrasonic endoscopy (page 7, lines 18-21 in the new revised manuscript).**

As the tumor diameter was one of the crucial factors in determining the type of surgery, we have added data to indicate the type of surgery based on the tumor diameter (page 7, lines 25-28 in the new revised manuscript), and discussed the possible therapeutic approaches and indications for the various treatments (page 11, lines 14-22 in the new revised manuscript).

RESPONSES TO THE EDITOR'S COMMENTS:

1) Methods section of the Abstract: It's too short. Please add it to 80 words. Thank you!

Response: **We have added further information to the Methods section to increase its length to just over 80 words.**

2) Results section of the Abstract: RESULTS (no less than 120 words): You should present *P* values where necessary and must provide relevant data to illustrate how it is obtained, e.g. 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$

Response: **We have added additional information to ensure the length of the Results section is over 120 words, and added further *P* values for the data summarized in this paragraph.**

3) A decomposable figure is required. It means that the fonts and lines can be edited or moved. The example is attached. The coordinate graphs supplied should be decomposable (each part of your figure could be moved so as to easily edited). You can send it as excel, word or powerpoint format so that I can edit them easily.

Response: **We have provided a Powerpoint file containing Figure 1, which we trust will be sufficient for your purposes. The Powerpoint figure is provided as a separate file, and has also been copied into the new revised manuscript.**

Other responses:

1. Text for the COMMENTS section of the manuscript has been included under the headings: *Background*, *Research frontiers*, and *Innovations and breakthroughs*.
However, we are uncertain what to add under the heading *Peer review*. While the reviewers provided important comments that we have addressed in our revision, there were no comments that most represent the characteristics, values and significance of the article as a whole. We have therefore not included any comments under this heading at this stage.

2. The references for the article have been checked and, where necessary, amended. The PMID and DOI numbers have, where applicable, been provided.

3. Number of references: In response to your request to include *at least 26 references*, we have modified the manuscript to include a further 17. Thus, the total number of references in the new revised manuscript is now 27.

Thank you again for considering our manuscript for publication in the *World Journal of*

Gastroenterology. We look forward to hearing from you soon regarding its acceptability for publication.

With kindest regards,

Yours sincerely

Jiangqiang Cai

Cancer Institute & Hospital
Chinese Academy of Medical Sciences
Beijing, 100021
P.R. China.