Format for ANSWERING REVIEWERS

October 22, 2016

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 30061 revised highlighted.doc).

Title: Pancreatic neuroendocrine tumor G1 patients followed up without surgery: Case series

Authors: Mitsuru Sugimoto, Tadayuki Takagi, Rei Suzuki, Naoki Konno, Hiroyuki Asama, Ko Watanabe, Jun Nakamura, Hitomi Kikuchi, Yuichi Waragai, Mika Takasumi, Satoshi Kawana, Takuto Hikichi, and Hiromasa Ohira

Name of Journal: *World Journal of Clinical Oncology*

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The manuscript has been improved according to the reviewers' suggestions, as follows:
1 The format has been updated

2 Revisions were performed according to the reviewers' suggestions

Reviewer 3475354
***Comment:* The manuscript by Sugimoto and colleagues reviews treatment options for G1 pancreatic neuroendocrine tumors (PNET). Thirteen patients with G1 PNET were included in this single center retrospective analysis, and eight were analyzed in detail. Obviously, this is a rather small cohort of patients, and it is very difficult to draw any clinical useful conclusion out of this. There is an ongoing debate of how to treat small (e.g. <1cm) PNETs. The present study does not add much novel information to this topic.**

Response: Thank you for your valuable comments. As you stated, the patient cohort was too small to justify only following up the NET patients without surgery. Therefore, we revised the title, certain sentences and the conclusion (title; Page 4, lines 3, lines 13-14, lines 18-19; Page 4, line 24- Page 5, line 1; Page 11, lines 15-17).

Reviewer 3077466
***Comment:* In this study, the authors are trying to evaluate whether it is possible to follow up a pancreatic neuroendocrine tumor (PNET) without surgery. Overall, this is a very good and valuable case series with solid experimental design. The study is novel and well written, the data are of high quality and the results support the authors' conclusion. Only three minor concerns are noted that can be easily addressed:**

1. In the Abstract and Core tip, there are two severe clerical errors. The first five patients should have surgery after follow-up, but in the context, the authors addressed without surgery.

Response: Sorry for our mistakes. We rewrote the text to state "with surgery" (Page 4, line 10; Page 4, line 21).

2. In the Discussion part, even though the authors have reviewed the risk factors for NETs to follow up without surgery, I am wondering whether the authors could address some specific risk factors for NET G1 to follow up without surgery, or provide some thoughts about what kind of NET G1 patients could be followed up without surgery.

Response: Sorry for confusing you. All risk factors derived from past reports. In this study, the number of patients was too small to indicate the original risk factors. We revised the relevant sentences (Page 10, line 15, line 24).

3. The images of figure 2 and 3 should have calibration bars.

Response: Thanks for your comment. After viewing the sample PDF sent to us, we added magnification values to the figure legends.

Reviewer 1221925

Comment: ***This is an interesting paper on whether patients with G1 pancreatic NET can be followed without surgery using a case series of patients. Could the authors please comment on the following:***

1) In the abstract the following needs to be changed so that the authors' point can be made clear: "The observation period for the five cases without surgery ranged from 6-80 months, and tumor growth was observed in one case. In contrast, the observation period for the three cases without surgery ranged from 17-54 months, and tumor growth was not observed."

2) Same comment for the Core Tip

Response to 1) and 2): Sorry for our mistakes. We rewrote the text to state "with surgery" (Page 4, line 10; Page 4, line 21).

3) How was it decided which patients would undergo surgery and which would only undergo follow-up? What were the criteria from switching a patient from follow-up to surgery?

Response: Thank you for valuable questions. We recommended surgery for all NET patients. However, if certain patients did not agree to surgery, we only performed a follow-up (Page 7, lines 10-12).

4) What do the authors recommend in terms of a) how do you decide which patients to follow-up and b) how often and how do you follow-up

Response: Thank you for the questions.

a) If patients did not agree to surgery, we only performed a follow-up (Page 7, lines 10-12).
b) Patients without surgery underwent dynamic CT or abdominal echo approximately 2 times per year, performed by an attending physician (Page 9, lines 4-5).

5) The small number of patients is a very significant limitation in terms of reaching any meaningful conclusions, as interesting as the authors' point may be.

Response: We agree. We revised the title, certain sentences and the conclusion accordingly (title; Page 4, lines 3, lines 13-14, lines 18-19; Page 4, line 24- Page 5, line 1; Page 11, lines 15-17).

Reviewer 3646552

Comment: ***nice paper. May in future , large case series can be published.***

Response: Thank you for your comment. We hope that a large case series will confirm our results.

Reviewer 3262127

Comment: Dear Authors! In all the time that I reviewed papers for WJG and company Journals, this paper was probably most difficult to review (more precisely, for its Decision part). On formal grounds, the work is done very good: the reviewed paper is a well organized, performed, and written research on actual topic. The language was carefully edited by a serious proofreading agency. However, I can not agree with the authors in the principal problem discussed in the article. In my personal opinion, in all pancreatic NETs, the right

treatment strategy is surgery. Why do I think so? There are three main arguments.

Response: Thank you for your valuable comments. We strongly agree with your opinion. All NETs should undergo surgery. We recommended surgery for all NET patients, but certain patients still did not agree to surgery. Therefore, we only followed up these patients. We added these facts to the manuscript (Page 4, lines 13; Page 6, lines 20-24; Page 7 lines 10-12; Page 11, lines 15).

1)Even modern diagnostic tools (as a fine-needle EUS-controlled biopsy) are not absolutely precise in their diagnostic accuracy in case of pancreatic tumor.

Response: Thanks for your comment. For NET G1, the accordance rate between specimens obtained by EUS-FNA and specimens obtained during surgery was 92.3% (36/39) in past reports. However, this value was high, and we agree that surgical grading is the gold standard (Page 11, lines 7-8, lines 10-11).

2)In course of time, pancreatic NETs (as NETs in general) can change their morphologic characteristics including mitotic count and so on.

Response: Thank you for your valuable comment. We added one more limitation, about mitotic count, to the manuscript (Page 11, lines 10-11).

3)Currently, all types of pancreatic resection can be performed safely with very good immediate results. In my own opinion, the most serious contraindication for surgery in pancreatic masses is bad general condition of a patient (and, possibly, an advanced age), but not tumor morphology itself. Hereby, I can not accept the thesis of safety of long-term observation in G1 pancreatic NETs. This is the reason why I can not give a positive decision on publication. However, I am aware that my opinion on this article may not be the ultimate truth.

Response: Thank you very much for reviewing our manuscript. We strongly recommended surgery to our NET patients; in this study, we wanted to detail what occurs if NET patients do not agree to surgery.

Thank you again for publishing our manuscript in the *World Journal of Clinical Oncology*.

Sincerely yours,
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