May 30, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 17016-review.doc).

Title: Recurrent gastric neuroendocrine tumors underwent total gastrectomy

Author: Myounghwa Jung, Jung-Wook Kim, Jae-Young Jang, Young Woon Chang, Sun Hee Park, Yong Ho Kim, Youn Wha Kim

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 17016

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer 1

(1) the basic situation of this patient should be shorten.

→ We agree with the reviewer's comment. We deleted following sentences.

" Upon admission at this time, the laboratory data were as follows. White cell count (WBC): 7600/*u*l, hemoglobin: 16.3 g/dl, platelets: 179000/*u*l, alkaline phosphatase: 83 U/l, aspartate aminotransferase (AST): 21 U/l, alanine transaminase (ALT): 21 U/l, blood urea nitrogen (BUN): 23 mg/dl, creatinine: 0.7 mg/dl, sodium: 135 mmol/l, potassium: 4.3 mmol/l, chloride: 100 mmol/l, and glucose: 154 mg/dl."

" The calcium level was 9.2 mg/dl, phosphorus, 3.1 mg/dl, and fasting glucose, 132 mg/dl."

(2) And I am wondering if the patient has a family history of cancer or stomach disease.

→ We appreciate your good question. The patient did not have any family history of cancer or stomach disease.

Reviewer 2

(1) The length of the text should be shortened, and the detailed data of blood examination in the "case report" section (page 4, initial paragraph) are not necessary

→ We agree with the reviewer's comment. We deleted following sentences.

" Upon admission at this time, the laboratory data were as follows. White cell count (WBC): 7600/*u*l, hemoglobin: 16.3 g/dl, platelets: 179000/*u*l, alkaline phosphatase: 83 U/l, aspartate aminotransferase (AST): 21 U/l, alanine transaminase (ALT): 21 U/l, blood urea nitrogen (BUN): 23 mg/dl, creatinine: 0.7 mg/dl, sodium: 135 mmol/l, potassium: 4.3 mmol/l, chloride: 100 mmol/l, and glucose: 154 mg/dl."

" The calcium level was 9.2 mg/dl, phosphorus, 3.1 mg/dl, and fasting glucose, 132 mg/dl."

(2) There are so many figures, and the authors should show only representative selected figures.

→ We agree with the reviewer's comment. We deleted figure 5 (immunohistochemical features of neuroendocrine tumor)

(3) Discussion section includes only general information regarding gastric NETs. Instead, the author

should described much more about the discussion points of their own case, and the general information should be omitted as much as possible.

→ We agree with the reviewer's comment. We delete following sentences which mentioned general Information.

"Type I gastric NETs generally present as small (less than 10 mm in diameter), multiple (68%), and polypoid (78%). The tumor cell is isomorphic and medium-sized, and mitosis is rarely seen. Ki-67 staining is less than 2%(Li, Qiu et al. 2014). Fortunately, Type I gastric NET is very rarely metastatic (< 5%). Type I NETs are characteristically minimally invasive with 27% limited to the mucosa, 64% only invading the mucosa and/or submucosa and only 9% invading the muscularis propria(Rindi, Bordi et al. 1996). Type II gastric NET, 5-6% of gastric NETs, occurs as a result of a gastrin-secreting neoplastic tissue in Zollinger-Ellison syndrome. Clinically, type II gastric NET has similar characteristics to type I gastric NET. However, Type III gastric NETs, 14-25% of all gastric NETs, are large (>2 cm), usually single, and not associated with hypergastrinemia or chronic atrophic gastritis. Type III is aggressive with deep invasion and metastasis, leading to a poor prognosis. Type IV gastric NET is a rare, single, large, and highly malignant tumor"

"Severe hyperplasia or dysplasia of ECL cells with chronic atrophic gastritis confined to the fundus-body of the stomach are risk factors in NET development"

"The stimulus of gastrin has been demonstrated to have a critical role in proliferative changes of ECL cells through a sequence of hyperplasia-dysplasia-neoplasia"

→ We also made best efforts to describe more about discussion point. We added following sentences.

"There is no definite guideline for the treatment of gastric NET, especially cases involving recurrence due to the low incidence of this condition and the lack of understanding of the pathogenesis of this disease. The European Neuroendocrine Tumor Society (ENETS) guidelines did not mention the management of recurrent gastric NETs(Delle Fave, Kwekkeboom et al. 2012). Basuroy R *et al.* vaguely recommended that tumors should be resected when possible(Basuroy, Srirajaskanthan et al. 2014). Crosby DA *et al.* insisted that in cases of NET recurrence after endoscopic resection, surgical resection, including wedge resection or antrectomy, is recommended. Total gastrectomy should be considered for the management of NET recurrence after minimally invasive surgery(Crosby, Donohoe et al. 2012). Definite guidelines for the treatment of recurrent gastric NETs are needed, because recurrence occurs frequently in type 1 gastric NET cases. Merola E. *et al.*(Merola, Sbrozzi-Vanni et al. 2012) reported that 63.6% of type 1 gastric NET cases experience recurrence after a median of 8 months, and 66.6% of these cases experience a second recurrence after a median of 8 months following carcinoid removal."

We also rearranged sentences, paragraphs to easy to understand our case report.

3 References and typesetting were corrected

We have revised our paper as described above. And we believe we have addressed all questions and comment, but would be happy to provide further information or revision if necessary.

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

Sincerely yours,

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