June 13, 2016

Dear Drs Ze-Mao Gong

Please find enclosed the edited manuscript in Word format (file name: 25569G&D-NETreview) and copyright assignment in PDF format.

Title: Management of gastric and duodenal neuroendocrine tumors

Author: Yuichi Sato

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 25569

The manuscript has been improved according to the suggestions of reviewers and editors:

1. Format has been updated. I attached the complete revised manuscript (25569- edited by Ysato) .

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

(1) Comment of Reviewer: (00761842)

1. Abstract paragraph 2 and page 9 – chemotherapy should only be considered for high grade type III G-NETs, not those (albeit rare) type III G-NETs that are grade 1.

Response:

Thank you for your suggestion. As you suggested, we corrected the abstract part and type III G-NETs part of "Treatment options for G-NETs" section in our document, as follows:

"Therefore, surgical resection and chemotherapy are generally necessary for Type III G-NETs, ."

and

"The ENETS guidelines recommend that type-III G-NETs be managed in the same manner as gastric adenocarcinomas. Therefore, these guidelines recommend surgical resection (partial or total gastrectomy with lymph node dissection) and chemotherapy

(34 ~~31~~).".

2. Introduction, page 4, line 2: the cell of origin of NETs in not known. The tumors may arise from gastrointestinal stem cells and then undergo neuroendocrine differentiation rather than arising from neuroendocrine cells per se. This statement should therefore be altered slightly to reflect that uncertainty.

Response:

According to your suggestion, we corrected our manuscript in the introduction part, as follows:

"Neuroendocrine tumors (NETs), which were first labeled as carcinoid tumors by Oberndorfer in 1907, are rare neoplasms that arise from the peripheral neuroendocrine system dispersed in various organs (1). ~~the neuroendocrine cells of the diffuse neuroendocrine system (1)~~."

3. Page 7, last paragraph of 'Classification and clinical features' section: I suggest pointing out that not all type III G-NETs with liver metastasis cause carcinoid syndrome. This is still a rare presentation as most G-NETs are not serotonin secreting.

Response:

According to your suggestion, we collected our manuscript in last paragraph of 'Classification and clinical features' section, as follows:

"The typical presentation of "carcinoid syndrome" including flushing, tachycardia, and diarrhea, occurs rarely in patients with gastric NETs (< 1%) and is almost exclusively associated with type III tumors, especially those presenting with liver metastasis ~~seen only with type III G-NETs presenting with liver metastasis~~ (3027~~)~~. It is not commonly associated with any other types of G-NET."

4. Page 9: 68Ga-DOTANOC-PET or similar scans are a more sensitive alternative to octreoscan.

Response:

According to your suggestion, we added the sentence at the last paragraph in the "Other investigatios" section, as follows:

"However, recent studies concerning PET in NETs using 68Ga-labeled PET tracers (68Ga-DOTATOC, -DOTANOC, and –DOTATATE) have shown promising results, with a higher rate of lesion identification and lower costs than usually achieved with octreoscan (35, 36). However, few studies have demonstrated the utility of 68Ga-labeled PET in patients with G-NETs (35, 36), and further studies would be

therefore required.".

5. Page 9-10: type I G-NETs: (a) Very small G1 type I G-NETs (especially <5mm) are probably best managed by surveillance particularly if the patient is elderly or has co-morbidities. This is currently not made clear. Endoscopic treatment in this setting is unlikely to be necessary, especially as the hypergastrinemia persists.

Response:

I agree with your suggestion. However, we previously reported that 4 patients with small TIGC (<1cm) were complicated with capillary invasion. Therefore, we added the sentence in "Type I G-NETs" part of "Treatment options for G-NETs" section, as follows:

"Several recent reports have revealed that no tumor-related deaths were observed in patients with type I G-NETs who were assessed by endoscopic surveillance but not treated (25, 40, 41). Therefore, endoscopic surveillance seems to be a reasonable approach in selected patients with type I G-NETs, such as small tumors in elderly patients or those with co-morbidities. However, we (25) have reported four patients with small TIGC (<1cm) that were complicated with capillary invasion (lymphatic invasion in two, venous invasion in two), so endoscopic follow-up without treatment must be selected after careful consideration"

(b) In view of the good prognosis of type I G-NETs whatever treatment is given, the statement that ESD is 'recommended' is not in my opinion warranted. There is no evidence to support this. Resection success rates may be better but overall patient survival may not be altered.

Response:

According to your suggestion, "currently recommended" was changed to "useful" in "Type I G-NETs" part of "Treatment options for G-NETs" section, as follows:

"Endoscopic submucosal dissection (ESD) is useful ~~currently recommended~~ for the removal of submucosal tumors including type I G-NETs."

(c) There are other medical options for type I G-NETs that are not commonly used but are probably worth mentioning. These include somatostatin analogues and CCK2 receptor antagonists (the latter is still experimental though).

Response:

Thank you for your suggestion. As you suggested, we noted somatostatin analogues and CCK2 receptor antagonists in the "Type I G-NETs" part in "Treatment options for

G-NETs" section in our document, as follows:

"Somatostatin analogues (SSAs), which inhibit G cell-mediated gastric secretion and reduce ECL cell hyperplasia, are effective in reducing the number and size of type I and II G-NETS (45-48 ~~36-39~~). However, the routine use of SSA is not recommended due to their short-term effects, recurrence following cessation of therapy (49 ~~40~~), and high treatment costs. Therefore, SSAs therapy should be limited to patients with recurrent or multifocal type I G-NETs (50). Recent report have revealed that intermittent treatment with SSAs would be safe and effective method of treating recurrent type I G-NETs in patients who do not undergo ER (51).

Netazepide (YF476), a potent gastrin/CCK-B receptor antagonist, has been reported to suppress gastric acid output and reduce serum CgA levels, in addition to the size and number of type I G-NET (52, 53). Therefore, netazepide is a potentially useful drug for the treatment for type I G-NET. However, the levels of CgA mRNAs recovered to pre-treatment levels after stopping treatment (53), so the long-term administration of natazepide needs to be assessed in the context of type I G-NETs."

6. Page 16, treatment of D-NETs: In some patients such as the elderly or those with co-morbidities who have small (<1cm) grade 1 duodenal NETs, is endoscopic surveillance a reasonable option? If so should this be reflected in Fig 3?

Response:

I agree with your suggestion. Therefore, we added the sentence in the "Treatment options for D-NETs", as follows:

"To date, endoscopic surveillance for D-NETs, even in cases of small G1 tumors, is not generally recommended because lymph node metastasis and microvascular invasion have been observed in such tumors (76-78). "

On the other hands, *figure3* is the management protocol of D-NETs by the ENETS guidelines, therefore, the figure cannot be changed at my own discretion.

7. Page 17, line 3: change surgically to surgical.

Response:

According to your suggestion, "surgically" was changed to "surgical" in "Treatment options for D-NETs" section, as follows:

"The management of intermediate-sized (1 to 2□cm) D-NETs is controversial. Large (> 2□cm) D-NETs or D-NETs of any size with lymph node involvement, should be treated by limited surgical ~~surgically~~ resection."

8. Table 2: Patients with type I G-NETs have low acid secretion hence HIGH gastric pH, whereas type II gastric NETs have high acid secretion and LOW gastric pH. Please correct.

Response:

I appreciate the reviewer's comment and corrected table 2:

(2) Comment of Reviewer: (03475231)

This article deserves for publication, but in the treatment of gastroduodenal gastrinomas articles they cited articles only from NIH group in USA. So I recommended authors to reade articles published from EU surgeons and Japanese surgeons. should cite two important articles published in this Jouranal from Japan, that is, Imamura M. Recent standardization of treatment strategy for pancreatic neuroendocrine tumors. World J Gastroenterol 2010;16:4519 ―4525 Imamura M, Komoto I, Ota S, Hiratsuka T, Kosugi M, Doi R, Awane M, Inoue N. Biochemical curative surgery for gastrinoma in multiple endocrine neoplasia type-1 patients. World J Gastroentrol 2011;17: 1343-1353 Their results different similar to EU experiences recommend the resection of duodenal gastrinomas either by Whipple operation or by duodenectomy with lymphnode dissection to achieve cure of gastrinoma in more than 80% of MEN1 with ZES in 16 patients.Besides they whowed that curative lymphadenectomy is possible because the positive nodes are less than 3 in most cases, and in about half of them negastive. Additionally a few articles are written below to make this review manuscript better by reading them carefully. Bartsh DK, et al. Pancreaticoduodenal endocrine tumors in MEN 1: surgery or surveillance? Surgery 2000;128:958-66. Barrtsh DK, Fenderich V, et al. Outcome of PD in patients with MEN 1. Ann Surg. 2005;242:757-66. Lairmore TC, Chen VY, et al. Diodenopancreatic resections in patients with MEN1. Ann Surg 2000; 231:909-18. Imamura M, Kanda M, Soga J, et al. Clinicopathological characteristics of duodenal gastrinomas. World J Surgery 1992;16:703-10. Giblril F, Venson DJ et al. Prospective study of natural history of gastrinoma in patients with MEN 1. J Clin Endocrinol Metab. 2001;86:5282-93. in which thet observed 57 cases and three died of disease and liver mets of gastrinoma took place about 23% of cases during 8 years. What is your opinion about these results.

Response:

In accordance with the reviewer's comment, I added the sentence in "Treatment options for D-NETs" section as follows:,

"However, several reports have documented that aggressive surgery increases survival (95) or prevents the development of liver metastasis (96). Imamura et al also reported that surgical curative resection, especially pancreas preserving total duodenectomy based on accurate localization using selective arterial secretagogue infection test, is useful for curing MEN1-ZES related duodenal gastrinomas (97,98).."

and attached the references, as follows;

95) Norton JA, Fraker DL, Alexander HR, Gibril F, Liewehr DJ, Venzon DJ, Jensen RT. Surgery increases survival in patients with gastrinoma. Ann Surg. 2006;244(3):410-9. PMID: 16926567; PMCID: PMC1856542.

96) Bartsch DK, Fendrich V, Langer P, Celik I, Kann PH, Rothmund M. Outcome of duodenopancreatic resections in patients with multiple endocrine neoplasia type 1. Ann Surg. 20050;242(6):757-64, PMID: 16327485; PMCID: PMC1409888.

97) Imamura M. Recent standardization of treatment strategy for pancreatic neuroendocrine tumors. World J Gastroenterol. 2010;16(36):4519-25.PMID: 20857521; PMCID: PMC2945482.

98) Imamura M, Komoto I, Ota S, Hiratsuka T, Kosugi S, Doi R, Awane M, Inoue N. Biochemically curative surgery for gastrinoma in multiple endocrine neoplasia type 1 patients. World J Gastroenterol. 2011;17(10):1343-53. doi: 10.3748/wjg.v17.i10.1343. PMID: 21455335; PMCID: PMC3068271.

(3) Comment of Reviewer: (02567522)

This article is easy to read. The short title describes it as a review of the management of gastric and duodenal NETs. However, it is not just a review; it is also a personal opinion of the authors on the endoscopic management of those tumours. The full title should reflect the fact that it is a review and personal opinion. As such, there's nothing new in the review content of the article. There are several other similar reviews in recent literature. However, the authors' experience should be useful to gastroenterologists and endoscopists in general, who are likely to see such patients. There's mention neither of recent literature on the prevalence of gastric NETs (Scand J of Gastroenterol 2015; 50: 550–559) nor the potential use of a gastrin/CCK2 receptor antagonist in the treatment of type 1 gastric NETs, which are gastrin-driven (Aliment Pharmacol Ther 2012; 36: 1067–1075; and PlosOne 2013; 8: e76462).

Response:

In accordance with the reviewer's comment, we changed the title, from "Endoscopic management of gastric and duodenal neuroendocrine tumors" to "Management of gastric and duodenal neuroendocrine tumors".

Moreover, we read and cited two suggested references, added the sentences in "Epidemiology" section of "Gastric Neuroendocrine Tumors (G-NETs)" section, and "Treatment options for G-NETs" section , as follows:

"In the latest data review, the prevalence was 3.4 and 1.7 per 100,000 people in 10 European countries and the US, respectively (12)."

"Netazepide (YF476), a potent gastrin/CCK-B receptor antagonist, has been reported to suppress gastric acid output and reduce serum CgA levels, in addition to the size and number of type I G-NET (52, 53). Therefore, netazepide is a potentially useful drug for the treatment for type I G-NET. However, the levels of CgA mRNAs recovered to pre-treatment levels after stopping treatment (53), so the long-term administration of natazepide needs to be assessed in the context of type I G-NETs."

(4) Comment of Reviewer: (00006950)

1. Section on pathology of the tumors should be included with particular role of staining of the neuroendocrine cell with chromogranin A and other markers. . Pathological classification of these tumors and neuroendocrine hyperplasia (for type 1 net) has been well developed and needs mention.

Response:

Thank you for your suggestion. As you suggested, we added the sentence in the "Classification and clinical features" section in "Gastric Neuroendocrine Tumors (G-NETs)", as follows:

"In immunohistochemical staining, NETs cells are positive for chromogranin-A (CgA), synaptophysin, vesicular monoamine transporter 2, and somatostatin receptor 2A (26). In particular, CgA staining is useful for observing hyperplastic and dysplastic ECL cell changes. ECL cell hyperplasia is characterized by more than six chains of linear hyperplasia per mm, and ECL cell dysplasia, occurring mainly in microinfiltrative lesions, is associated with increased risks of G-NETs. (27)"

2. Drug therapy with Octreotide LAR for gastric neuroendocrine tumor type 1 has been well studied. Paper gives no mention of that.

Response: Thank you for your suggestion. As you suggested, we noted Octreotide LAR, which is Somatostatin analogues (SSAs), in the "Type I G-NETs" part in "Treatment options for G-NETs" section in our document, as follows:

"Somatostatin analogues (SSAs), which inhibit G cell-mediated gastric secretion and reduce ECL cell hyperplasia, are effective in reducing the number and size of type I and II G-NETS (45-48 36-39). However, the routine use of SSA is not recommended due to their short-term effects, recurrence following cessation of therapy (49 40), and high treatment costs. Therefore, SSAs therapy should be limited to patients with recurrent or multifocal type I G-NETs (50). Recent report have revealed that intermittent treatment with SSAs would be safe and effective method of treating recurrent type I G-NETs in patients who do not undergo ER (51)"

3. Antrectomy is an option for recurrent gastric type 1 tumors. Authors do mention it but lacks critical evaluation and references. Authors should consider these points to make this review broad based and valuable.

Response: In accordance with your suggestions, we corrected the point that we described about antrectomy, as follows:

"Among the surgical options, antrectomy is an option for recurrent type-I G-NETs. Antrectomy alleviates G-cell-mediated hypergastrinemia resulting in EDL cell hypertrophy. However, it may not be effective in preventing recurrence or metastasis (42). Moreover, surgical therapy is more invasive and associated with higher risks of complications (42). However, patients treated with antrectomy have a lower risk of recurrence and need fewer follow-up EGDs than patients who receive endoscopic resection or EGD surveillance alone (43). Laparoscopic antrectomy may provide a minimally invasive alternative surgical treatment for type-I G-NETs (43, 44). Therefore, in cases of recurrence or persistent G-NETs after ER or local resection, antrectomy or partial/total gastrectomy, along with lymph node dissection, is needed

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

Sincerely yours,

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