Format for ANSWERING REVIEWERS

March 29, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 16547-review.doc).

Title: Advantage of Endoscopic Mucosal Resection with a Cap for Rectal Neuroendocrine Tumors ORIGINAL ARTICLE Retrospective Study

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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

(1) reviewer 02438888

Thank you for your comments. Your concise explanations are including all of our opinions.

(2) reviewer 00068723

A. This study is retrospective study and all with lesions >10 mm were removed by ESD. And we checked the size by EUS, the type of procedure is influenced by endoscopists. So mean tumor size was smaller in EMR-C group than ESD group. But, subgroup analysis by tumor size(<5mm and 5-10mm) showed that there was not a significant differences in tumor size between EMR-C and ESD groups.

B. As you mentioned, selection criteria of EMR-C or ESD is vague due to retrospective study. We performed endoscopic procedure alternatively, if possible, for tumors < 10mm. I statemented that it was not randomized in the limitation.

C. More information on NET, clinical course, introduction of EMR-C and merit were revised and added in introduction.

(3) reviewer 02544032

As you mentioned, this study is a non-randomized retrospective study performed in one hospital and its results and conclusions have definite limitations. I look forward to validating our results in prospective randomized controlled studies.

(4) reviewer 02823396

Thank you for your comments.

(5) reviewer 01714224

Thank you for your comments.

A. Was NET histotype established prior to or following endoscopic resection? How many NETs were malignant and how many benignant? Did patients with a malignant NET undergo other staging

investigations or chemotherapy or other treatments? How patients were followed up, performing clinical visit, radiological investigations, other? Authors should take into account all these points to reach a conclusion about adequacy of endoscopic procedures they compared.

Most of them were not histotype established prior to procedure. Our study demonstrated a rate of metastasis of 0.92 % (1 of 109 patients). Lymphovascular invasion was found in one patient with a 6 mm tumor treated with ESD. The patient required additional surgical therapy. We focused on endoscopic procedures in this manuscript. We followed up patients every six months for two years, and then yearly thereafter. We checked general condition, CT and colonoscopy (or sigmoidoscopy). I inserted this sentence in discussion.

B. Authors reported that all polyps were examined by EUS. Is EUS assessment a their routine policy for all polyps, especially when the lesions is <5 mm in size? Such a policy seems to be time consuming, especially in the clinical practice when a diminutive polyp is generally removed by a biopsy forcep. Authors should explain this choice in a non prospective setting study.

I agree with you. Becauses of rectal NETs usually appear as submucosal lesion, we were examined by EUS to estimate the size and the depth of invasion. But, we founded that all of the lesions is <5 mm in size were not invaded muscle. So, now we realize EUS is not required for the small NETs.

C. More than half of all polyps (63/116) were <5 mm in size, and 13/63 were removed by ESD. Authors should clarify the reason why these diminutive polyps have been removed by ESD. Did Authors reach a pre-procedure histological diagnosis of NET or EUS show an invasive neoplasm in such 13 diminutive polyps?

We did not evaluation histology prior to procedure. Although the reason was not accurate, more deeper mass in submucosa were removed by ESD. Please understand this study is a non-randomized retrospective study.

D. Authors should explain the reason why endoscopic resection was complete in 100% versus histological resection in 53% of the lesions <10 mm in size. This discrepancy seems to be particularly surprising when ESD was adopted.

Endoscopic resection was complete in 100%, but histological resection was in 71% of the 5mm < lesions <10 mm in size. We think that during ESD, the use of electrocautry may damage the tumor margins, this is the main cause of high rate of histological incomplete resection.

E. Authors should furnish data regarding outcome of patients (metastases and survival rate) treated with EMR in comparison to those undergone ESD. Data should be stratified according to lesion size.

Our study demonstrated a rate of metastasis of 0.92 % (1 of 109 patients). Lymphovascular invasion was found in one patient with a 6 mm tumor treated with ESD. The survival rate were 100 % in both groups. There was no recurrence during a mean follow up period of 720 days. Follow up periods according to lesion size were inserted in table 3.

F. In Table 2 Authors reported that ESD allowed to reach a complete histological resection in 40/51 (78.4%) of lesions, 35 of them having <10 mm in size (see Table 4). Thus, ESD failed in two

lesions >10 mm in size. Authors should furnish possible reasons of incompleteness in all occurred cases, above all with lesions >10 mm.

ESD did not fail in two lesions >10 mm in size, the lesions were removed by ESD successfully. But, they had incomplete histologic resection margin, in other words one has positive vertical margin, and the other has positive lateral indeterminate margin. I found my mistake the number of indeterminate margin (Table 2). I corrected to Vetical;Lateral: Vet & Lat =2:1:0 vs 1:3:2 at table 2.

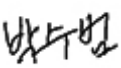
G. Majority of polyps (109/116, 94%) measured <10 mm and only 7 were >10 mm. As Authors reported in Introduction, the risk of metastases has been reported to be 0–10% (but differently in Discussion they stated 1.7-10%) for tumors <10 mm and 4–30% for tumors 10–19 mm in diameter. As requested in point 1, how many NETs were malignant? It is possible that the number of malignant NETs, together with the number of lesions >10 mm, is too small to reach a conclusion regarding the possible advantage of EMR compared to ESD in the resection of NET.

The risk of metastases was corrected to about 0-10% in discussion. Our study demonstrated a rate of metastasis of 0.92 % (1 of 109 patients). Lymphovascular invasion was found in one patient with a 6 mm tumor treated with ESD. In case of NETs > 10mm in size, there was no malignant tumor in our study.

3 References and typesetting were corrected

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

Sincerely yours,



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