Author's response to reviews

Title: The clinical features and treatment modality of esophageal neuroendocrine tumors: multicenter study in Korea

Authors:

Chang Geun Lee (sanailcg84278427@gmail.com)
Yun Jeong Lim (limyj@dongguk.ac.kr)
Seun Ja Park (parksi@ns.kosinmed.or.kr)
Byung Ik Jang (jbi@med.yu.ac.kr)
Seok Reyol Choi (sychoi@dau.ac.kr)
Jae Kwang Kim (ikkim4881@hanmail.net)
Yong-Tae Kim (yongtkim@snu.ac.kr)
Joo Young Cho (schcjy@schmc.ac.kr)
Hoon Jai Chun (drchunhj@chol.com)
Si Young Song (sysong@yuhs.ac)

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Author's response to reviews: see over
Thank you very much for giving us an opportunity to revise our manuscript. Comments by the reviewers have proved very useful in improving the quality of this article. The revisions are based on the reviewers’ comments and we respond to them point by point.

We requested missing data at each research institution once again after late notice of review result (May, 22th, 2014) and moreover; it takes long time to acquire data again after re-requesting. We are very sorry to delay the response of revision. Hopefully, you can understand our concerns about delayed revision and we really hope that these changes now make this paper acceptable for publication. The changes are in Red in the text, in the revised manuscript. Thank you in advance for your attention to our manuscript.

Sincerely yours,

Chang Geun Lee, M.D.,

Yun Jeong Lim, M.D., Ph.D.
Editor's Comments:

1) Patient selection criteria was not well defined: define inclusion and exclusion criteria. Table 3 lists that 9 patients had missing pathologic diagnosis. Please describe the missing not applicable in more detail? How was the diagnosis of NET made?

**Answer:** Thank you for the kind comment. Following your advice, we added inclusion and exclusion criteria in “Material” section (line 65-69, page 4)

 Ł Inclusion criteria were all pathologically confirmed NETs of esophagus, regardless of the quality of pathologic reports and histologic classification.

 Ł Exclusion criteria included the followings: (1) the clinical data are not available in spite of the pathologic report that prove the NET of esophagus.

 Ł (2) patient had a history of neuroendocrine carcinoma elsewhere.

 We requested the missed the 9 pathologic data at each research institution again and the pathologic confirmation for NET was obtained. However, several pathologists did not mention their “histologic type” in the pathology report. We added this limitation in “Discussion” section (line 261-264, page 14) following as

 Ł First, different pathologist at each institution diagnosed esophageal NETs.

 Ł Because the international consensus has not been achieved for histologic classification of esophageal NETs, some pathologists did not mention their histology type.
2) Description of radiologic and endoscopic findings is difficult to understand. It needs more clarification and assurance that the data are consistent.

Answer: Thank you for the kind comment. Following your advice, we corrected radiologic and endoscopic findings and removed uncertain data. (line 122-132, page 7-8)

The endoscopic findings of the 26 cases of primary esophageal NETs are summarized in Table 2. The primary tumor was most frequently located in the lower esophagus (18 patients, 69.2%), followed by the middle esophagus (4 patients, 15.4%) and upper esophagus (2 patients, 7.7%). Two patients had no information that specify the location of the lesion in the esophagus. The tumor was mainly represented in a single lesion (24/26, 92.3%), and only 2 cases (7.7%) were found to have multiple lesions. The sizes of the tumors ranged from 0.5cm to 7.5cm (mean 2.34± 1.63 cm; median 1.9cm). These tumors mostly represented elevated polypoid or nodular elevated type (17/26, 65.4%). The overlying surface showed mostly smooth, glistening and tan-brown discoloration. Some other tumors were represented large infiltrative lesion within the esophageal wall by elevated and depressed type (6/26, 23.1%) or ulcerated type (3/26, 11.5%). Disease metastasis was assessed by anatomical imaging including computed tomography (CT) (15/26, 57.7%), endoscopic ultrasound (EUS) (7/26, 26.9%), ultrasonography of the abdomen (2/26, 7.7%), and positron emission tomography (PET) scan (7/26, 26.9%).
4) Clinical data on treatment: how metastatic disease was confirmed?

**Answer:** Thank you for the comment. Following your advice, we added more information in “Method” section (line 78-82 page 4) following as

- Regional LN metastasis or distant metastasis was mainly evaluated by imaging modalities including computed tomography (CT), endoscopic ultrasound (EUS), etc. If the metastasis was uncertain, biopsy was performed at the suspected site. If operation had been taken, metastasis was confirmed by post operation pathologic report.

5) Edit data listed to make sure all data are consistent (eg. paragraph on EUS: 7 pts had EUS but then only 3(100%) had hypoechoic findings.)

**Answer:** Thank you for the kind comment. Following your advice, we corrected radiologic findings and removed uncertain data. (line 122-132, page 7-8)

6) Check grammar and paragraph structure.

**Answer:** Thank you for your kind comment. Following your advice, some revisions have been made by professional proofreading agency. However, if you judge that this paper need the English proofreading more, we are willing to send this paper to other agency for publication.

7) Nationwide is used in the title. I think nationwide in this study means representative of Korean population. But, your data was not randomly selected from
general population. Thus, I think the term nationwide in the title is not appropriate.

What do you think about that?

Answer: Thank you for your comment. Through neuroendocrine tumor registry in the Korean society of gastrointestinal cancer, esophageal neuroendocrine tumors were collected. Many institutions (over forties) were participated in the registry of gastrointestinal neuroendocrine tumor. Following your advice, we revised the title as follows.

The clinical features and treatment modality of esophageal neuroendocrine tumors: multicenter study in Korea

8) In background, you conducted multicenter study to find the accurate incidence rate of esophageal NETs. I don't think the incidence of esophageal NETs can be obtained in your study. What do you think about that?

Answer: Thank you for your kind comment. Through the gastrointestinal neuroendocrine tumor registry in the Korean society of gastrointestinal cancer, 26 esophageal NETs (1.3%) among 2037 gastroenteropancreatic NETs were collected. We requested the missed the 9 pathologic data at each research institution again and the repeated pathologic confirmation for NET was obtained. Following your advice, we corrected the “Introduction” (line 56-58, page 3) and “Result” (line 110-111, page 7) section as following:

Thus, this multicenter study was undertaken to assess incidence, clinical characteristics, treatment modality, and prognosis of esophageal NETs.
We collected 2,037 pathology reports of patients with gastroenteropancreatic NETs. Among them, 26 cases (1.3%) were observed in the esophagus.

9) In endoscopic findings, the tumors exhibited elevated polypoid or nodular elevated, depressed or ulcerated features. Could you add more information of endoscopic findings of esophageal NETs in your study? Could you describe the surface color of tumor in endoscopic findings? 

Answer: Thank you for your kind comment. Following your advice, we added more detail information about endoscopic findings in “Result” section (line 129-132 page 7-8)

The overlying surface showed mostly smooth, glistening and tan-brown discoloration. Some other tumors were represented large infiltrative lesion within the esophageal wall by elevated and depressed type (6/26, 23.1%) or ulcerated type (3/26, 11.5%).

10) How many cases did you get the final diagnosis only though endoscopic biopsy?

Answer: Thank you for your kind comment. We added more information in “Result” section (line 149-151 page 8) following as

The seventeen patients (65.4%) got the final diagnosis by only endoscopic biopsy. Three patients got the final diagnosis after the endoscopic removal of the tumor and six patients got the final diagnosis after operation.
11) In the discussion section, ref 17 was incited to show the correlation of NET size and patient’s prognosis. As you know, ref 17 deals with rectal carcinoid tumor. I think biological behavior of esophageal NETs may be different from that of rectal NETs.

What do you think about that?

*Answer:* Thank you for the accurate comments. We also agree your opinion. Following your advice, we leave out this [reference 17] and revised our manuscript.

(line 216-219, page 12)

There are no data about prognostic factors association with the esophageal NETs. Kaplan-Meier survival analysis of this study showed that size is an important prognostic factor. More than 2.0 cm in size appeared to be significant poor survival and widespread metastasis of esophageal NETs were all related to more than 2.0cm in tumor size.
Referee 1

Major

1. Patient selection criteria was not well defined: define inclusion and exclusion criteria. Table 3 lists that 9 patients had missing pathologic diagnosis. These patients can't be included in analysis

Answer: Thank you for the kind comment. Following your advice, we added inclusion and exclusion criteria in “Material” section (line 65-69, page 4)

Inclusion criteria were all pathologically confirmed NETs of esophagus, regardless of the quality of pathologic reports and histologic classification.

Exclusion criteria included the followings: (1) the clinical data are not available in spite of the pathologic report that prove the NET of esophagus. (2) patient had a history of neuroendocrine carcinoma elsewhere.

We requested the missed the 9 pathologic data at each research institution again and repeated histopathologic confirmation for NET was obtained,

2. Why 2000 WHO classification was used? Was this to compare differences in diagnosis over 10 year period? Staging and classification part of this study is not explained. Which staging system (WHO vs AJCC) is most predictive of clinical outcome?

Answer: Thank you for the kind comment. In this study, the esophageal NETs had been enrolled in the registry from 2002 to 2012. Most of them had been pathologically diagnosed before the 2010. Thus, either AJCC 7th classification or
2010 WHO classification had not been applied. We added more information following as (line 264-268, page 14)

- Second, the 2000 WHO classification system was mainly used in this study. This is because most of the pathologic reports were made before the 2010 WHO classification. However, to our knowledge, this study regarding the 26 cases of esophageal NETs demonstrated the largest case numbers and long-term follow-up period enough to give the valuable clinical information.

3. Description of radiologic and endoscopic findings is difficult to understand. It needs more clarification and assurance that the data are consistent.

**Answer:** Thank you for the kind comment. Following your advice, we corrected radiologic and endoscopic findings and removed uncertain data. (line 122-132, page 7-8)

- The endoscopic findings of the 26 cases of primary esophageal NETs are summarized in Table 2. The primary tumor was most frequently located in the lower esophagus (20 patients, 76.2%), followed by the middle esophagus (4 patients, 15.4%) and upper esophagus (2 patients, 7.7%). Two patients had no information that specify the location of the lesion in the esophagus. The tumor was mainly represented in a single lesion (24/26, 92.3%), and only 2 cases (7.7%) were found to have multiple lesions. The sizes of the tumors ranged from 0.5cm to 7.5cm (mean 2.34± 1.63 cm; median 1.9cm). These tumors mostly represented elevated polypoid or nodular elevated type (17/26, 65.4%).
The overlying surface showed mostly smooth, glistening and tan-brown
discoloration. Some other tumors were represented large infiltrative lesion
within the esophageal wall by elevated and depressed type (6/26, 23.1%) or
ulcerated type (3/26, 11.5%).

4. Clinical data on treatment: how metastatic disease was confirmed? There should be records specifying biopsy (if done), and these should be specifically noted. If metastatic disease was not pathologically verified it invalidates any chemotherapy date (and disease related survival).

Answer: Thank you for the kind comment. We added more information in “Method” (line 78-82 page 4) section following as

Regional LN metastasis or distant metastasis were mainly evaluated by imaging modalities including computed tomography (CT), endoscopic ultrasound (EUS), etc. If the metastasis was uncertain, biopsy was performed at the suspected site. If operation had been taken, metastasis was confirmed by post operation pathologic report.

5. Overall. There is a lot missing data to draw conclusions. The most that can be concluded is incidence based on definite pathologic reports 0.8% after all non confirmed cases excluded.
Answer: Thank you for the kind comments. Following your advice, we corrected main manuscript and removed uncertain data. We requested the missed the 9 pathologic data at each research institution again and the histopathologic confirmation for NET was obtained.

Minor

1. Re-design tables: there is a lot of duplicated data in table 4.

Answer: Thank you for the kind comment. We removed table 4 and added figure 1.

2. Edit data listed to make sure all data are consistent (eg. Paragraph on EUS: 7 pts had EUS but then only 3 (100%) had hypoechoic findings.)

Answer: Thank you for the kind comment. Following your advice, we corrected radiologic findings in “Result” section and removed uncertain data.
3. Check grammar and paragraph structure.

**Answer:** Thank you for your kind comment. Following your advice, some revisions have been made by professional proofreading agency. However, if you judge that this paper need the English proofreading more, we are willing to send this paper to other agency for publication.
Referee 2

1. There are only 26 cases of esophageal NETs that the authors attempt to discuss. There are several typographic, grammar, and linguistic errors throughout the manuscript.

Answer: Thank you for your kind comment. Following your advice, some revisions have been made by professional proofreading agency. However, if you judge that this paper need the English proofreading more, we are willing to send this manuscript to other agency for publication.

2. The adjuvant chemotherapy administered across patients was admittedly varied and therefore is neither clinically discernible nor meaningful.

Answer: Thank you for the kind comment. Adjuvant chemotherapy had been undertaken according to variable clinical situations including the age, performance scale, economic status, preference for treatment, etc. We also agree that inexistence of adherence of recommended treatment in these case series. Therefore, clinical response and patient survival could not be accurately evaluated. However, the overall sample size of this study is largest one considering rare esophageal NETs and we struggled to demonstrate the information regarding the clinical behavior, prognosis or treatment response as much as possible. We drew the Figure 3 to suggest the valuable information by organizing treatment strategies from these collective cases.
3. Immunostaining technique and tissue handling is not discussed; the variation in primary anti-body binding affinity, the secondary anti-body processing, and the differences in the various stains used area all additional variants to the interpretation of these data

**Answer:** Thank you for the kind comment. Following your comments, we added more information in “Discussion” section (line 224-229, page 12) as following

In previous studies, there were inconsistent results about whether synaptophysin and chromogranin expression is associated with better prognosis. One Korea multicenter study reported synaptophysin and chromogranin expression was not significant prognostic factors [1]. However, in only appendix NETs, they represented synaptophysin was associated with better prognosis [1]. In this study, we performed survival analysis for
esophageal NETs, but synaptophysin and chromogranin were not prognostic factors.

4. In so much as that this manuscript is a collection of 26 different cases over a decade in a region that employed clinically disparate management algorithms for biologically different tumors, that resulted in unique treatment strategies yielding the said results—therefore attempting to draw any sort of meaningful clinical information from these collective cases is challenging.

Answer. Thank you for the kind comment. To our knowledge, the management algorithm for esophageal NETs has not been defined yet due to the rare incidences of esophageal NETs. Especially in the advanced esophageal NETs, decision regarding treatment had been undertaken according to variable clinical situations including the age, performance scale, economic status, preference for treatment, etc. We also agree that inexistence of adherence of recommended treatment in these case series. We drawed the Figure 3 to suggest the valuable clinical information by organizing treatment strategies from these collective cases.
Esophageal neuroendocrine tumor

< 1.0 cm
- Well differentiated
- Regional LN metastasis (-)
- Lymphovascular invasion (-)
  Endoscopic resection

≥ 1.0 cm

- Regional LN metastasis (+)
  Surgical resection + adjuvant chemotherapy ± radiotherapy or palliative chemotherapy

- Regional LN metastasis (-)
  Palliative chemotherapy (mainly cisplatin + etoposide)

- Widespread metastasis
  Surgical resection ± adjuvant chemotherapy
Referee 3

1. Nationwide is used in the title. I think nationwide in this study means representative of Korean population. But, your data was not randomly selected from general population. Thus, I think the term nationwide in the title is not appropriate. What do you think about that?

*Answer:* Thank you for your comment. Through neuroendocrine tumor registry in the Korean society of gastrointestinal cancer, esophageal neuroendocrine tumors were collected. Many institutions (over forties) were participated in the registry of gastrointestinal neuroendocrine tumor. Following your advice, we revised the title as follows.

The clinical features and treatment modality of esophageal neuroendocrine tumors: multicenter study in Korea

2. In background, you conducted multicenter study to find the accurate incidence rate of esophageal NETs. I don’t think the incidence of esophageal NETs can be obtained in your study. What do you think about that?

*Answer:* Thank you for your kind comment. Through the gastrointestinal neuroendocrine tumor registry in the Korean society of gastrointestinal cancer, 26 esophageal NETs (1.3%) among 2037 gastrointestinal NETs were collected. Following your advice, we corrected the “Introduction” (line 56-58, page 3) and “Result” (line 110-111, page 7) section as following:
Thus, this multicenter study was undertaken to assess incidence, clinical characteristics, treatment modality, and prognosis of esophageal NETs.

We collected 4,951 pathology reports of patients with gastroenteropancreatic NETs. Among them, 26 cases (1.3%), was observed in the esophagus.

3. In endoscopic findings, the tumors exhibited elevated polypid or nodular elevated, depressed or ulcerated features. Could you add more information of endoscopic findings of esophageal NETs in your study? Could you describe the surface color of tumor in endoscopic findings?

Answer: Thank you for your kind comment. Following your advice, we added more detail information about endoscopic findings in “Result” section (line 129-132 page 7-8)

The overlying surface showed mostly smooth, glistening and tan-brown discoloration. Some other tumors were represented large infiltrative lesion within the esophageal wall by elevated and depressed type (6/26, 23.1%) or ulcerated type (3/26, 11.5%).

4. How many cases did you get final diagnosis only through endoscopic biopsy?

Answer: Thank you for your kind comment. We added more information in “Result” section (line 149-151 page 8) as following
The seventeen patients (65.4%) got the final diagnosis by only endoscopic biopsy. Three patients got the final diagnosis after the endoscopic removal of the tumor and six patients got the final diagnosis after operation.

5. In the discussion section, ref 17 was incited to show the correlation of NET size and patient's prognosis. As you know, ref 17 deals with rectal carcinoid tumor. I think biological behavior of esophageal NETs may be different from that of rectal NETs. What do you think about that?

Answer: Thank you for the kind comments. We also agree your opinion. Following your advice, we leave out this [reference 17] and revised our manuscript. (line 216-219 page 12)

There are no data about prognostic factors association with the esophageal NETs. Kaplan-Meier survival analysis of this study showed that size is an important prognostic factor. More than 2.0 cm in size appeared to be significant poor survival and widespread metastasis of esophageal NETs were all related to more than 2.0cm in tumor size.