[12/24/2020]

Lian-Sheng Ma
Editor-in-Chief
World Journal of Gastroenterology

Dear prof. Lian-Sheng Ma and dear reviewers:

Re: Manuscript ID: 60839 and Title: Clinicopathological features and prognostic factors associated with gastroenteropancreatic mixed neuroendocrine non-neuroendocrine neoplasms in Chinese patients

Thank you for your letter and the reviewer's professional and enlightening comments concerning our manuscript entitled "Clinicopathological features and prognostic factors associated with gastroenteropancreatic mixed neuroendocrine non-neuroendocrine neoplasms in Chinese patients " (ID： 60839). Your professional attitude and pertinent comments have given us great encouragement.Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The responds to the reviewer's comments and the main corrections in the paper are as flowing:

1. Responds to the reviewer's comments:

   Reviewer #1:

   1.1 Comment 1: The Authors report a large experience with endoscopic removal of rectal carcinoid. They had observed a complete resection rates by precutting endoscopic mucosal resection or by endoscopic submucosal resection and did not found any local or distant recurrence at the follow-up. They are to be commended for these excellent results.

   Response: Thank you for your summary and approval. We really appreciate your efforts in reviewing our manuscript. We have revised the manuscript accordingly. Our point-by-point responses are detailed below.

   1.2 Comment 2: A comment on the natural history of the small rectal carcinoid would be helpful: can a neuroendocrine tumor with Ki-67 index <3% became a neuroendocrine carcinoma? In other words, considering that the 10% at least of small rectal carcinoids recurred with a metachronous NET, how often a rectal NEC is found? This data could be useful to indicate the follow-up and the need to remove other neuroendocrine lesions.

   Response: Thank you for your professional reviews and opinions.This is indeed an enlightening question and an area that we need to pay more attention to. Our point-by-point responses are detailed below.

   i. In our study, the Ki-67 index of primary tumors in patients with metachronous

NET recurrence and metastasis were both >3% (Ki-67 index was 10% in one case and 5% in the other case). Also, only 20 patients with Ki-67 index <3% and no recurrence or metastasis was observed during follow-up. In other words, we did not find that carcinoid patients with Ki-67 index <3% had metachronous NEC recurrence during the follow-up process (we have added more specific follow-up results in the result description section, page7, line34).

ii. Possible cause: Carcinoid is the most common gastrointestinal neuroendocrine tumor. Even in the presence of metastatic disease, the degree of malignancy is very low [1]. Rectal carcinoids usually appear as small and localized tumors and rarely recur after resection. Therefore, rectal carcinoids have the best prognosis among all carcinoids [2-4]. According to the literature,Risk factors for gastrointestinal carcinoid metastasis include size >10 mm in diameter, muscular invasion, poorly differentiated neuroendocrine histology, lymphovascular involvement, and Ki-67 labeling index > 3% [5]. These further indicate that rectal carcinoids with Ki-67 index <3% have a good prognosis. This study did not find that Ki-67 index <3% of rectal carcinoids recurred with metachronous NEC during the follow-up process, which is consistent with the above-mentioned literature.

iii. Our research still has certain limitations: First, we were unable to fully evaluate possible confounders, owing to the retrospective nature of this study. Second, further follow-up studies are required to more accurately define their long-term outcomes. The third limitation is the limited presented data and the number of patients enrolled. As you said, this data could be useful to indicate the follow-up and the need to remove other neuroendocrine lesions. Therefore, a well-designed, multicenter, prospective trials with large samples should be performed to confirm these results in the future research. We will continue to pay attention to and discuss this issue in subsequent research. Thanks again for such instructive comment.

[1].Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD, et al.Current status of gastrointestinal carcinoids. Gastroenterology 2005; 128: 1717–51.

[2].Kumar AS, Sidani SM, Kolli K, Stahl TJ, Ayscue JM, Fitzgerald JF, et al.Transanal endoscopic microsurgery for rectal carcinoids: the largest reported United States experience. Colorectal Dis. 2012;14(5):562–6.

[3].Hamada Y, Tanaka K, Tano S, Katsurahara M, Kosaka R, Noda T, et al.Usefulness of endoscopic submucosal dissection for the treatment of rectal carcinoid tumors. Eur J Gastroenterol Hepatol. 2012;24(7):770–4.

[4].Niimi K, Goto O, Fujishiro M, Kodashima S, Ono S, Mochizuki S, et al.Endoscopic mucosal resection with a ligation device or endoscopic submucosal dissection for rectal carcinoid tumors: an analysis of 24 consecutive cases. Dig Endosc. 2012;24(6):443–7.

[5] Sugimoto S, Hotta K, Shimoda T, Imai K, Y amaguchi Y , NakajimaT, et al. Ono H (2016) The Ki-67 labeling index and lymphatic/venous permeation predict the metastatic potential of rectal neuroendocrine tumors. Surg Endosc 30(10):4239–4248.

2. Main corrections in the paper:

2.1 5 issues you raised

2.1.1 I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s).

Response: Thank you for your question. We have uploaded the funding agency copy of approval documen in the file destination of " 60839-Approved Grant Application Form(s) or Funding Agency Copy of any Approval Document(s) " .

2.1.2 I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Response: Thank you for your question.We have uploaded original figure documents and tables in the file destination of " 60839-Figures.ppt " and " 60839-Tables.docx " .

2.1.3 I found the authors did not write the "article highlight" section. Please write the "article highlights" section at the end of the main text.

Response: Thank you for your question. This is indeed our negligence. We have added the corresponding part to the revised manuscript in accordance with the writing requirements of the article highlights and marked it in red font(page 12).

2.1.4 Please provide an audio core tip file where the core tip content is recorded.

Response: Thank you for your question. We have uploaded audio core tip file in the file destination of " 60839-Audio Core Tip " .

2.1.5 Please provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement.

Response: Thank you for your question. We have uploaded the two files in the file destination of " 60839-Conflict-of-Interest Disclosure Form " and " 60839-Copyright License Agreement " .

2.2 Other corrections (All corrections are marked in red in the manuscript)

2.2.1 Page 1,line 11(The name of one of the authors)

We have corrected Nin-Ning Yang to Ning-Ning Yang.

2.2.2 Page 1,line 29 (The author's initials in the author's contribution have been revised in accordance with the writing regulations.)

Version before modification: Author contributions: YCH collected the clinical

data and prepared the manuscript; YCH and NY designed the study and supervised the statistical data; YCH and HC designed the research and contributed to the analyses; YLH, WY, RY, NL, SZ, and PY provided clinical advice; ZF made the pathologic diagnosis and supervised the report.

Revised version: **Author contributions:** Huang YC collected the clinical data and prepared the manuscript; Huang YC and Yang NN designed the study and supervised the statistical data; Huang YC and Chen HC designed the the research and contributed to the analyses; Huang YL , Yan WT , Yang RX , Li N , Zhang S , and Yang PP provided clinical advice; Feng ZZ made the pathologic diagnosis and supervised the report.

2.2.3 Page 19,Figuer 1

We have corrected all (,) in the annotations of Figure 1 to (;)

Version before modification:

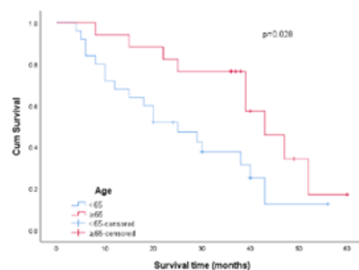
Figure 1. Histopathological and immunohistochemical findings of GEP-MiNEN.
A: Neuroendocrine carcinoma (left) and adenocarcinoma (right) (HE staining, scale bar 200 μm). B: Adenocarcinoma component (HE staining, scale bar 200 μm). C: Neuroendocrine component (HE staining, scale bar 100 μm). D: CK-positive adenocarcinoma (EnVision, scale bar 100 μm). E: CgA-positive neuroendocrine (EnVision, scale bar 100 μm); F: Syn-positive neuroendocrine (EnVision, scale bar 100 μm).

Revised version:

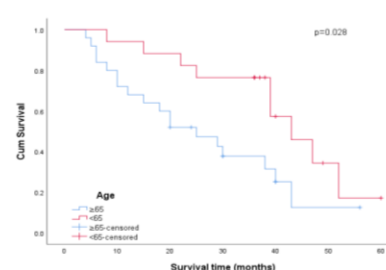
Figure 1. Histopathological and immunohistochemical findings of GEP-MiNEN.
A: Neuroendocrine carcinoma (left) and adenocarcinoma (right) (HE staining, scale bar 200 μm); B: Adenocarcinoma component (HE staining, scale bar 200 μm); C: Neuroendocrine component (HE staining, scale bar 100 μm); D: CK-positive adenocarcinoma (EnVision, scale bar 100 μm); E: CgA-positive neuroendocrine (EnVision, scale bar 100 μm); F: Syn-positive neuroendocrine (EnVision, scale bar 100 μm).

2.2.4 Page 20,Figuer 2(We found an error in the A picture and replaced it. In addition, the A-K pictures have been replaced with a clearer version.)

Picture A before correction:



Picture A after correction:



2.2.5 Page 23,Table 4

Ⅰ: We have corrected (<20) to(>20). (line13,below the Ki-67 index)

before correction:

Ki-67 index
< 2
2–20
< 20

after correction:

Ki-67 index
< 2
2–20
> 20

Ⅱ: We have corrected (0.054)from the original wrong position to its next line.(The last number in the third row from the bottom of the table 4)

before correction:

Mean	49.3	34	28.6		0.054
Follow-up				< 0.001	
Dead	3	34	27		
Alive	44	7	15		

after correction:

Mean	49.3	34	28.6		
Follow-up				< 0.001	0.054
Dead	3	34	27		
Alive	44	7	15		

2.2.6 The remaining red fonts represent grammatical errors that we corrected after careful inspection. We are very sorry for the trouble caused to you.

We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in World Journal of Gastroenterology.Thanks again to the reviewer for his/her evaluation comments and your hard work for the publication of our paper.Looking forward to your reply. Wishing you and your family a very merry Christmas!

Sincerely.

Yuchen Huang.

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