

Answering Reviewers letter

Dear reviewers and editors:

Thank you for your efficient work in procession of our manuscript entitled " Analysis of 72 Patients with Colorectal High-Grade Neuroendocrine Neoplasms from Three Chinese Hospitals " (Manuscript No:49942). We also really appreciate the dear reviewers for giving us precious advices, which are important for us to improve the quality of our work. Our study focused on clinicopathologic features and prognostic factors of colorectal High Grade Neuroendocrine Neoplasms (HGNENs), which are a rare and aggressive malignant disease. Many issues, such as their classification and therapy strategies, have been controversial for a long time. In previous WHO classification and nomenclature for colorectal HGNENs, all colorectal HGNENs are regarded as poorly-differentiated. However, colorectal HGNENs with good morphologic differentiation were also reported in some literatures. There is a trend to categorize colorectal HGNENs with good morphological differentiation as a subgroup different from high-grade neuroendocrine carcinomas (HGNECs) in the newest WHO classification. We introduced this classification into our study and compared the prognoses of different subgroups.

In addition, we have carefully revised our paper based on the comments of reviewers, and the point-to-point responses to the reviewers' comments are presented below:

Reviewer #1

Comment 1: The retrospective nature of the study.

Response: We really agree with this comment. Indeed, colorectal HGNENs are an extremely rare disease and the prospective study of this group of disease is hard to achieve. To date, no prospective researches of colorectal HGNENs can be found in the literature. Most previous reports were case reports or retrospective study with small samples. We conducted a multicenter retrospective study and enrolled 72 cases, which included more cases than most previous reports. We also realized the shortcoming of the retrospective nature of our report and discussed it at the end of our article. We hope a prospective study that include more centers can be conducted in future.

Comment 2: Is there any case reports of functional neuroendocrine tumors in the colon, and what is the clinical presentation in those patients

Response: We really appreciate this advice, which helps improve the quality of our paper significantly. In fact, carcinoid syndromes can hardly be seen as most of these tumors are nonfunctional and cannot secrete 5-hydroxytryptamine. To date, only several cases with hormonal symptoms have been reported in the literature. These patients presented symptoms such as facial flushing, sweating and diarrhea due to excessive production of hormones. Moreover, carcinoid syndromes were usually observed in cases with liver metastasis.

Comment 3: is there a difference in the endoscopic feature between colonic neuroendocrine tumors and the other types of colonic tumors?

Response: For early and small lesions, colorectal HGNENs usually present typical endoscopic features that are different from colorectal adenocarcinomas. They arise in the deeper layers of the intestinal mucosa and appear as smooth sessile lesions with normal overlying mucosa. Yellow mucosal discolouration might be observed in cases with positive expression of chromogranin. However, most cases present large and advanced lesions at the date of diagnosis, these lesions show no significant different endoscopic presentations with other colorectal tumors.

Comment 4: some corrections in the uploaded file.

Response: Thanks for the kind reminding, we checked our uploaded files again and had the errors modified already in the newly uploaded files.

Finally, we really appreciate your hard and efficient work, every piece of advice is truly precious for us to improve the quality of our work.

With kind regards,

Yours sincerely