Milan, 2021-12-22

Dear Editor,

Thank you for your interest in considering a revised version of our manuscript.

Please find herewith enclosed a copy of our revised manuscript No. 72437 entitled "Rectal neuroendocrine tumors: current advances in management, treatment, and surveillance."

Thank you very much for going into depth with our paper, we are happy that you've noticed all the strengths and weaknesses. Thank you for your constructive criticism that substantially improved the paper. We believe that all concerns have been successfully rebutted.

We hope the revised version will now be suitable for publication in the *World Journal of Gastroenterology*.

Here is our point-by-point response to your comments:

POINT TO POINT RESPONSE

Reviewers' comments:

Reviewer #1:
Scientific Quality: Grade D (Fair)
Language Quality: Grade C (A great deal of language polishing)
Conclusion: Major revision
Specific Comments to Authors: The authors report rectal neuroendocrine tumors. The report has a very important aspect and is interesting, however, there are the following concerns: Major comments The manuscript is written in great detail, but that is why it is hard to focus. The novelty and purpose of this manuscript are difficult to find. For a systematic review, there seems to be a bias in the selection of papers.
We thank the Reviewer for his constructive criticism. We better focused on the novelties in the conclusion session (see page 27, lines 3-9; page 28, lines 18-26).
Our manuscript is a proposal for the section "Minireviews", not a systematic review, in which case it would have certainly emerged biased in the selection of papers, as highlighted by the Reviewer.

Minor comments
#1 The submission rules of World Journal of Gastroenterology need to be followed.
We reformatted the manuscript according to the submission rules.

#2 It is necessary to review whether the article citations are appropriate.
It has been done.

#3 In the paragraph of risk factors for metastases, progression, recurrence, these aspects are confusing including Table 1.
This paragraph has been completely revised as for Table 1.

#4 In 'LOCALIZEDDISEASE', the expression of 'thanks to' is too friendly.
Thank you for the suggestion. We corrected it.

#5 Figure 4 needs to explain the procedure and legend in more detail for readers to understand.
Thank you for the suggestion. We explained the device and the procedure in detail (see page 28, lines 15-20).

#5 In case that Figure 5 is citation, the citation needs to be specified in the legend. In addition, the permission of posting need to be confirmed.
Figure 5 is an original picture made by us; therefore, we don't need any permission to publish it. The citation refers to the content of the picture, according to the ENETS guidelines.

Reviewer #2:
Scientific Quality: Grade E (Do not publish)
Language Quality: Grade B (Minor language polishing)
Conclusion: Rejection
Specific Comments to Authors: In recent years, the number of patients with NETs has been increasing, but there is not much knowledge about rectal NETs. While this reviewer believes that the authors summarized the latest findings on rectal NET, some points should be addressed prior to publication. In particular, I think terminology issues need to be correct.
Major comments:
Although the authors use the term NEN frequently, the WHO defines NEN as a term consisting of NETs, which are well differentiated, and NECs, which are poorly differentiated. Since NETs and NECs are often considered separately in clinical practice, the authors need to be aware of this in their structure.
We thank the reviewer for the clarification. A statement to clarify this classification and nomenclature has been added in the introduction (see page 6, lines 3-6). The general principles of the new classification of neuroendocrine tumors as reported in the 5th series of WHO classification of digestive system tumors, based on a consensus meeting in Lyon, divided NEN into NET and neuroendocrine carcinomas (NEC) based on their molecular differences. This has been added also in the "RISK FACTORS FOR INCIDENCE, METASTASES, PROGRESSION, RECURRENCE" section (see page 11, lines 2-7).

Minor comments: 1) In the CLINICAL PRESENTATION AND ENDOSCOPIC APPEARANCE section (Page 2, Line 11-12), authors described rectal NETs as arising from the submucosal layer, however, rectal NENs are epithelial neoplasms, not submucosal neoplasms.
This sentence has been reformulated, explaining that rectal NETs are epithelial lesions, with submucosal development, without invading the muscolaris propria (see page 7, lines 2-7, 15, 21-28).

2) This reviewer believes that the TEM section (Page 12, Line 3- Page13, Line 2) is difficult to understand the content. Since the selection criteria for TEM are not clearly defined, it would be easier to understand the content if the advantages, disadvantages, and controversial points are described separately.

We thank the Reviewer for the suggestions. We explained more in detail the advantages and disadvantages of TEM and, thus, the best-suited indications for this technique (see page 19, lines 1, 2, 5-9, 19-26).

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The authors provide a systematic analysis of the current status of rectal Neuroendocrine tumors (NETs). While the manuscript is comprehensive and clear, some points should be addressed. 1. The authors provided risk factors for metastasis, progression and recurrence. However, they did not provide risk factors on which population may be at risk for rectal NETs and therefore surveillance. I suggest adding a paragraph on the baseline risk factors for rectal NETs as there have been several large-scale studies on the subject (Ko et al, Surg Endosc. 2017 Oct;31(10):3864-3871, Pyo et al, J Gastroenterol. 2016 Dec;51(12):1112-1121).

We thank the Reviewer for this observation and, as suggested, we added a paragraph regarding risk factors for the development of r-NENs (see pages 9, lines 2- 12) with pertinent references (#21, 22, 23, 24).

2. Suspicion of rectal NETs before resection are important on the clinical decision making of how to treat them. It has been reported that patients whose rectal NETs were diagnosed or suspected as NETs before resection showed a much higher complete resection rate than those whose tumors were resected as polyps and then diagnosed (Moon et al, Am J Gastroenterol. 2016 Sep;111(9):1276-85). As this is clinically very important, please consider adding this.

We thank the Reviewer for their suggestion. In the "EPIDEMIOLOGY OF RECTAL NEUROENDOCRINE TUMORS" section, a paragraph dedicated to these observations has been added (see page 7, lines 3-7).

3. Though the authors submitted an English editing Certificate, there are still some areas in the manuscript which are awkward. Please have the English grammar and context looked at again.

A careful revision of the language grammar and context has been performed.

Reviewer #4:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: First of all, it's a great honor to receive the invitation. This article describes the research progress of rectal neuroendocrine tumors in recent years from the aspects of epidemiology, diagnosis and treatment. Especially in the treatment

part, it explains the diversity of treatment of rectal neuroendocrine tumors from the perspectives of endoscopy, surgery and medical treatment. Here are some of my suggestions: 1、Since the treatment of advanced rectal neuroendocrine tumors or rectal neuroendocrine tumors with distant metastasis is mentioned later, imaging diagnosis and other related contents (CT, MRI, PET-CT, etc.) should be added to the previous diagnosis part. For intermediate and advanced tumors, imaging diagnosis is particularly important.
This is a right suggestion by the Reviewer, therefore a specific paragraph has been added in the first part of the section "SYSTEMIC THERAPIES FOR ADVANCED DISEASE" (see page 21, lines 2-12).

2、The final summary should not only repeat the problems mentioned above, but also put forward new ideas and comments on the next research of the disease clock, so as to sublimate the whole article.
We thank the Reviewer for this advise to revise our conclusions. We enriched them by adding our prefiguration of the future perspectives (see page 27, all).

3、It is noted that your manuscript needs careful editing by someone with expertise in technical English editing paying particular attention to English grammar, spelling, and sentence structure so that the goals and results of the study are clear to the reader.
As previously mentioned, technical English has been deeply revised.

We thank you for your attention and look forward to hearing from you at your earliest convenience.

Yours truly,

Sara Massironi, MD PhD

Correspondence information:

Sara Massironi

Division of Gastroenterology,

San Gerardo Hospital,

Via Pergolesi 33,

20900 Monza (MB),

Italy

Tel. +39-039-2332317; Fax: +39-039-2300129;

email: s.massironi@asst-monza.it