Milan, 26th April 2021

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 entitled "**GASTRINOMA AND ZOLLINGER ELLISON SYNDROME: A ROADMAP FOR THE MANAGEMENT BETWEEN NEW AND OLD THERAPIES**" following the amendments and changes as suggested by the Editors and the Reviewer. We would like to thank them for the thorough analysis. The comments and requests helped us to improve the manuscript and to provide the readers with further details on the study.

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

Our point-to-point response is with this letter.

We thank you for your continuing consideration and we look forward to hearing from you at your earliest convenience.

Yours truly,

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POINT TO POINT RESPONSE

Reviewer's comments:

Reviewer #1:
I carefully read the manuscript "GASTRINOMA AND ZOLLINGER ELLISON SYNDROME: LIGHTS AND SHADOWS", which is an overview of clinical presentation, diagnosis and management of Zollinger-Ellison syndrome and its cause that is mostly represented by pancreatic or duodenal gastrinomas. In the first part the authors well described the clinical features of this disease and all the diagnostic tools available, highlighting the most recent ones and the better way to use it. They also trying to define the best diagnostic workup (clearly showed in figure 1) which minimise the delay in the final diagnosis.

We thank the Reviewer for his/her positive comments.

Conversely, the last part, although it is clear and well written, do not add any new findings to the previous literature about this topic. In particular, what is described for the advanced disease is the treatment of metastatic neuroendoscrine tumors in general and not specifically of gastrinomas, which is also already well known and extensively reported in previous publications. So, this manuscript may be considered for publication only after a major revision. The authors have to better point out what is new about the treatment of zollinger Ellison syndrome and gastrinomas in particular for the localised stage, whose management may significantly differ from other NET histologies.

We thank the Reviewer for this correct observation. As reasonably suggested, the section focused on metastatic disease (see the paragraphs "*Liver-Directed Therapies" and "Anti-proliferative treatment")* has been shortened as it is general and well-known from previous reports. In fact, there are only a limited number of studies specifically addressing the treatment of ZES patients with advanced disease, and most data comes from series with patients with all the different NENs, gastrinomas included. We also added some brief sentences which specifically refer to gastrinoma (see "Surgery", "*Liver-Directed Therapies" and "Anti-proliferative treatment", s*entences in yellow).

For what matters the localized stage, the combination of PPIs which resolve symptoms and surgery for definite cure represents the hallmark of gastrinoma treatment. As per Reviewer's suggestion, we have better pointed out what is specific/new about the treatment of ZES; in details, :

- **in the Abstract we highlighted that "For the localized stage, the combination of proton pump inhibitory therapy which usually resolves symptoms and surgery, whenever feasible, with curative intent represents the hallmark of gastrinoma treatment."**

- **in the "Conclusions", we added a pertinent comment which highlights both the leading role of PPI treatment and surgery in the management of ZES and the changes in the role of surgery: "For what regards the treatment of the localized disease the two milestones are represented by PPIs for symptoms' control and surgery with curative intent. The role of surgery in the treatment of gastrinoma has changed completely from the introduction of PPIs. In the past, total gastrectomy represented the sole effective treatment to treat ZES by removing the end-organ target of gastrin.**

With the use of PPIs , gastric hypersecretion was no longer considered a problem and surgical excision started to be proposed as a potentially curative therapy".

Finally, we mentioned the potential role of CCK2R-antagonists as anti-secretory agents and inhibitors of the development of enterochromaffin-like (ECL) cell-tumors in animals (see the bottom of the paragraph "*Antisecretory medications"),* however strong evidence is lacking supporting their use in the human setting; a pertinent reference has also been added (#85).

In addition to this the authors have to:

1) modify manuscript title with a more appealing one which better explains what is described in the text;

We thank the Reviewer for this suggestion and we edited the title as follows: "**GASTRINOMA AND ZOLLINGER ELLISON SYNDROME: A ROADMAP FOR THE MANAGEMENT BETWEEN NEW AND OLD THERAPIES**".

2) on line 10 of the paragraph "Surgery" modify the sentence "The study, published in the New England Journal of Medicine.." deleting the name of the journal (which is described in the reference) and directly write the study results;

The sentence has been edited according to the Reviewer's suggestion.

Science editor:

(1) The "Author Contributions" section is missing. Please provide the author contributions;

This missing section has been added as follows (see page 2).

" Author contributions: Rossi RE designed the research; Rossi RE, Elvevi A, Citterio D, and Massironi S performed the literature search and wrote the first draft of the paper; Rossi RE, Massironi S, Coppa J, Invernizzi P, and Mazzaferro V reviewed for important intellectual content; Rossi RE and Massironi S wrote the final version of the paper; all the authors approved it."

(2) The authors did not provide original pictures. 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.

The original Powerpoint figures have been added as requested.