

To: BPG Editorial Board

Athens 26 June 2021

Dear Editors,

Thank you for your June 16th, 2021 letter. We would like to thank the reviewers for their comments and suggestions on our manuscript.

We have the pleasure to submit our revised manuscript entitled: "Trimodality treatment in Gastric and Gastroesophageal junction cancers: Current approach and future perspectives " to your distinguished journal for publication. In response to the suggestions made by you and the reviewers, we would like to inform you that we took into thoughtful consideration and addressed all the constructive suggestions and revised the manuscript accordingly using coloured text and track changes.

We would like also to state the significance and uniqueness of this work in the author's view. All authors contributed significantly to all stages of this work, they have read and approved the manuscript and confirm that no conflict of interest exists.

We hope that you will find the revised form of the manuscript to be improved and acceptable for publication the World Journal of Gastrointestinal Oncology.

We are looking forward to hearing back from you soon!

Kindest Regards,
Nikolaos Charalampakis

Responses to the Reviewers' Comments:

Reviewer #1

Specific Comments to Authors: Nice article. Congratulations.

Author Response and Action Taken: **We would like to thank the reviewer for his comment.**

Reviewer #2

Specific Comments to Authors: Dear authors: The manuscript is about the trimodality treatment in gastric and gastroesophageal junction cancers. In general, it introduces some current treatments and ongoing clinical studies. But it is regrettable that there exist significant weaknesses which need to be revised.

1. In "Treatment" part, the logical relationship among sub-headings is confused. For example, on page 7, in "Synergy of chemotherapy and radiotherapy - The role of immunotherapy" part, the authors mainly described the combination treatment of surgery, radiotherapy and

chemotherapy, so this sub-heading and the header content are obviously inappropriate. Therefore, the authors should list the several main modes of trimodality treatment, and then describe them in turn.

Author Response and Action Taken: **Headings have been changed and the text has been adjusted according to the reviewer's suggestions.**

2. In "Histology" part, the authors should supplement the relationship between esophageal carcinoma and gastroesophageal junction carcinoma, and then describe the histological features.

Author Response and Action Taken: **This part has been supplemented according to reviewer's suggestions.**

3. At the end of the text, the authors should discuss their prospects of this field.

Author Response and Action Taken: **The conclusion part has been changed to better reflect current prospects in trimodality treatment of gastroesophageal cancer.**

4. There are some spelling and grammar mistakes in the text that need to be corrected (see attached files).

Author Response and Action Taken: **The manuscript has been proof-read again.**

5. Please write numbers in Arabic numerals or English, do not mix.

Author Response and Action Taken: **All numbers were converted to Arabic numerals.**

Reviewer #3

Specific Comments to Authors: Charalampakis and colleagues performed a comprehensive review on previous study and current progress on the treatment GC and GEJC. The review is generally well-written with few grammar mistakes or typos, and provides a panorama on treatment of the specific cancers. The article is well-organized with clear structure and appropriate language. There are only some minor corrections, as listed below:

1. Page 2: 'understanding has improved of phenotypic and genotypic correlations', of should be on?

Author Response and Action Taken: **Corrected**

2. Page 3: is there any environmental or genetic factors for diffuse type?

Author Response and Action Taken: **An explanation has been added to the text.**

3. Page 5, last paragraph: What is the significance of molecular subtyping in therapy, especially immunotherapy?

Author Response and Action Taken: **The information has been added to the manuscript, according to reviewer's suggestions.**

4. Page 6, last paragraph: 'can be classified according to the Siewert classification, in type I', in should be into?

Author Response and Action Taken: **Corrected**

5. Page 7, first line: 'wheras' should be 'whereas'

Author Response and Action Taken: **Corrected**

6. Page 7, 'wheras D2 is when all N1 and N2 nodes (distant perigastric nodes and nodes along main arteries supplying the stomach) are removed (25). ' please rephrase the sentence.

Author Response and Action Taken: **The sentence has been rephrased.**

7. Page 8, 2nd line : Should provide the details on response improvement.

Author Response and Action Taken: **The synergy of radiation and immunotherapy is based mainly upon preclinical data, while results from large comparative randomized clinical studies are currently coming up. Nevertheless, an example of improved responses from a preclinical study has been added to the text.**

8. Page 8, 2nd paragraph: 'addition of radiotherapy', is this combination or sequential?

Author Response and Action Taken: **Most studies use concurrent chemotherapy and radiation. However, chemotherapy may precede or follow chemoradiation, depending on the design of the study.**

9. Page 8, 2nd paragraph: Why some patients did not receive post-surgical adjuvant therapy, which should be a routine for T3 patients.

Author Response and Action Taken: **This is the first study to evaluate the benefit of adjuvant chemoradiation in patients with gastric cancer. Enrolment took place from 1985 to 1996 and at this time, adjuvant chemotherapy had not yet cemented its role in the curative setting of gastric cancer.**

10. Page 9, 3rd paragraph: is preoperative hypoalbuminemia an independent risk factor? is it a predictive marker?

Author Response and Action Taken: **Hypoalbuminemia has been used as a prognostic marker for clinical outcomes and overall survival in a wide array of solid tumors, correlating with performance status and patient's comorbidities.**

11. Page 11, 2nd paragraph: a summary of main findings should be added.

Author Response and Action Taken: **A summary has been added.**

12. Page 11, 4th paragraph: Was there any benefit using radiotherapy? Need to brief the results.

Author Response and Action Taken: That was a non-comparative study so it is unclear whether clinical outcomes occurred due to chemotherapy or radiotherapy, or whether they would differ if patients received chemotherapy alone.

13. Page 17, 1st paragraph: a summary is needed for this section as there are many studies

Author Response and Action Taken: A summary has been added.

14. Page 18, 1st paragraph: a summary is needed.

Author Response and Action Taken: A summary has been added.

15. Page 20, 1st paragraph: a summary is needed.

Author Response and Action Taken: A summary has been added.

16. Page 23, 2nd paragraph: a summary is needed.

Author Response and Action Taken: A summary has been added.

17. Page 25, conclusion: The role of radiotherapy is one main focus of the review, should make conclusions on radiotherapy.

Author Response and Action Taken: The conclusion part has been changed to reflect suggestions made by the reviewers.

Reviewer #4

Specific Comments to Authors: Charalampakis et al. reviewed the existing data on trimodality approaches for gastric and gastroesophageal junction cancers, they also made comments on the remaining questions and presented the current research effort addressing them. This is a good review. I suggest the number of authors are reduced to no more than five. The language needs polishing a little bit.

Author Response and Action Taken: All the authors contributed significantly to the creation of this manuscript, either by collecting data, writing or reviewing the text and we think that they should all be included in the final work.

Science Editor

Issues raised:

(1) I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout; (2) the author should number the references in Arabic numerals according to the citation order in the text. The reference numbers will be

superscripted in square brackets at the end of the sentence with the citation content or after the cited author's name, with no spaces.

Author Response and Action Taken: **References have been adjusted to the format required by BPG.**