World Journal of Gastroenterology

Date 28/04/2019

Dear editor,

Subject: Submission of revised manuscript **47487**.

Thank you for your enclosing the reviewers' comments. We have carefully reviewed the comments and revised our manuscript accordingly. Our responses are given in a point-by-point fashion below. Changes to the manuscript are in red color in the manuscript text (the track changes function was used to demonstrate both delete segments and new inputs).

We hope that the revised manuscript is deemed suitable for publication in your esteemed journal and look forward to hearing from you.

Sincerely,

Dr Dimitrios Filippou MD, PhD

Response to Reviewer #1 (Reviewer's Code: 00071054):

We thank the reviewer for his/her thorough and careful reading of our manuscript and appreciate the insightful comments which help to improve its quality. Our response follows (the reviewer's comments are in *italics)*.

1. *Please explain the reason why patients with head and neck neoplasms were excluded from this study. It is well known that those were likely to develop*

concurrently with esophageal cancer and affect the extent of organ resection and lymph node dissection and the type of reconstruction.

Response: Our reasoning behind the decision to exclude patients with head and neck malignancies was that head and neck neoplasms represent a very diverse group of neoplasias (laryngeal, pharyngeal, tongue, etc.) that exhibit different biologic behaviors and varying degrees of responsiveness to chemoradiation. Definite chemoradiation therapy presents a viable alternative to surgery for these patients. In the present systematic review we decided to include only second primary neoplasms for which surgical excision is mandatory for achieving a good oncologic outcome, and for which chemoradiation alone is less beneficial.

2. *Patients who had concurrent neoplasms of the esophagus and the stomach were common in the clinical practice. Other type of reconstruction was reported in the following paper. Please confirm. "Kanda T. et al. Pedunculated gastric tube interposition in an esophageal cancer patient with prepyloric adenocarcinoma. World J Gastrointest Oncol 2011;3(5):75-8 [PMID: 21603033, DOI: 10.4251/wjgo.v3.i5.75]"*

Response: The type of reconstruction performed by Kanda et al. was identical to the one described by Songping et al. (reference #49). Nevertheless, we included the paper in our analysis and changed the results accordingly.

3. *Intraoperative cryoablation for kidney neoplasm was not a surgical resection; therefore, should be excluded from this study.*

Response: As suggested by the reviewer, we removed intraoperative kidney cryoablation from our analysis.

4. *Discussion was redundant and should be written more concisely.*

Response: As suggested by the reviewer, the discussion section was restructured in order to remove redundancies and provide a more compact and concise overview.

5. *Reference numbers were incorrectly given in several places. Please confirm.*

Response: Following the reviewer's comment we examined each individual reference. Misplaced references were fixed and redundant ones removed.

Response to Reviewer #2 (Reviewer's Code: 03259574):

We thank the reviewer for his/her thorough and careful reading of our manuscript and appreciate the insightful comments which help to improve its quality. Our response follows (the reviewer's comments are in *italics)*.

1. *The abstract is less concise, less informative and less representative regarding the whole content of manuscript.*

Response: Following the reviewer's comment, the abstract was restructured in hopes of being more concise and representative of the manuscript.

2. *The objective of the study should be clearly reformulated in the abstract.*

Response: As suggested by the reviewer the objective of the study was reformulated in the abstract.

3. *The introduction is too longer and the number of references is important (N=27), so , please ,shorten the introduction with decreasing the number of reference.*

Response: As suggested by the reviewer, the introduction was shortened and the number of references used was decreased.

4. *In Materials and Methods section: - Articles written in non –English language have been excluded from the study, regarding the reduced number of included studies in this work (n=23) and patients (n=117), including non-English papers may increase the number of both studies and patients . - The material and methods section should not contain any reference*

Response: When conceptualizing the study design, we collectively decided to exclude articles written in non-English language. The reason for this was twofold; firstly, because during our systematic search the non-English studies we encountered were mainly in the Japanese language which none of the authors speaks or understands. Secondly, through our study we sought to create a helping tool for physicians treating patients with coexisting esophageal and other neoplasms. In that context, we decided that all included studies should be in English language so that when future readers referred to them, they would find them to be in a familiar and understandable language. The reference in the material and methods section was removed.

5. *Explain what do you mean by peripheral gastrectomy in "(2) Non-anatomic gastric resection refers to gastric preserving gastrectomy other than total/subtotal/peripheral/distal gastrectomy [28]".*

Response: By the term peripheral gastrectomy we were referring to excision of the stomach in its distal part (in essence synonymous to distal gastrectomy). We decided to remove it to avoid any misconceptions.

6. *The Results section should not contain any reference; the results are not well presented.*

Response: The results section contains only references to the studies included in the analysis. Following the reviewer's comment, we removed all references in the results section, except the ones in the "study and patient characteristics" subsection. We acknowledge that the result section is densely written and although we endeavored to restructure it in a more presentable manner, the sheer diversity and number of procedures involved precludes a more concise presentation. Taking this into account, we elected to use visual aids (such as Tables) to illustrate the results in a more reader-friendly way.

7. *Discussion section: - The discussion is not well structured and some materials should not be in the end of discussion such as "Collectively, the data suggested that synchronous resection was safe, feasible and associated with low perioperative mortality (stomach: 4/81, lung: 1/18, pancreas: 0//6, colon/rectum: 0/2, kidney: 0/6, liver: 0/3), and as well as "Overall, our results support the safety and feasibility of synchronous esophagectomy and resection of other primary malignancies [59]". - There are much redundant sentences.*

Response: As suggested by the reviewer, the discussion section was restructured in order to remove redundancies and provide a more compact and concise overview.

8. *The number of non-anatomic gastric resections were important (n= 53), probably, in order to use the remained stomach as graft for reconstruction. So more informations are needed regarding the oncologic results of patients. - Details on the preoperative therapies (chemo and radiotherapie) for colorectal and gastric secondary neoplasm have not been provided .*

Response: Initially we thought to design the study so as to acquire solid oncologic data regarding the included patients. Regrettably, when we concluded our systematic search we discovered that oncologic outcomes were sparsely reported and data on preoperative and postoperative therapies were lacking or were reported with such heterogeneity (as stated in the limitations paragraph of the discussion section) that conclusions could not be reached by using them. Despite these difficulties gross patient outcomes are presented in Table 3 of our study.

9. *Detailed informations are needed on the two-stage surgical procedure employed in some patients.*

Response: Detailed information on two-stage procedures were omitted to reduce the length of the manuscript, taking into consideration the fact that the surgical technique was not different from single stage procedures performed for the same types of neoplasias. A brief mention is included in the discussion section.

10. *Regarding the several important limitations of the included studies in the present systematic review, it is so difficult to draw an accurate conclusion. Therefore the final conclusion should be reformulated.*

Response: As per the reviewer's suggestion the final conclusion was reformulated.

11. *Some references should be formatted correctly - The following cited references "52,53,54,56,58,59"do not match well with the subject and the objectives of the study.*

Response: The references number 52, 54, 56 and 59 (numbering in the initial manuscript draft) were removed as suggested by the reviewer. References #53 and #58 provide information on long-term functional and pain outcomes

following esophagogastrectomy, supporting that combined esophageal and gastric resections are both feasible and tolerable by the patients.

Response to Reviewer #3 (Reviewer's Code: 02922607):

We thank the reviewer for his/her time reading our manuscript and appreciate the kind remarks.