

The Editor,  
World Journal of Gastroenterology

**Further Revisions to Manuscript:** Systematic review of cytoreductive surgery and intraperitoneal chemotherapy for colorectal cancer peritoneal metastases: The next frontier in treatment of advanced disease

**Manuscript reference:** 6016

**Dear Editor,**

Thank you for the positive comments made by the Reviewers and the suggested changes.

We are grateful for the feedback and have now addressed all the recommendations in the following document and revisions.

The recommendations made have all been followed fully, are described below, and the relevant sections highlighted in the manuscript.

Please therefore find below a point by point response to the reviewers comments with reference made to the alterations in the revised manuscript.

We hope you will consider our manuscript for publication, and please contact us if you would like any further information.

With kind regards,  
Yours sincerely,



Alex Mirnezami

### **Comments by reviewer 1:**

1. *“As the authors pointed out most of the evidence to support the use of CRS and HIPEC comes from single institution studies. It is plausible that a treatment with significant morbidity is offered only to*

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*most healthy patients. In this scenario, a selection bias may well be responsible for the survival advantage found in this case control studies."*

We completely agree with reviewer 1 and have sought to address this in our manuscript by thoroughly and transparently describing the limitations of the existing studies. This is now covered in greater detail in the abstract, in the Results section entitled "Literature search and description of studies" – pages 10-11; "Patient selection" – pages 11-12; and in particular in the discussion section, pages 19-20.

2. *"The authors state in their conclusion: "nevertheless these consistently demonstrate survival rates greater than any available alternative justifying an aggressive approach". This reviewer does not feel that we have the evidence to definitively state that. Indeed NCCN guidelines only recommend CSR + HIPEC in the context of a clinical trial. Moreover this is not even discussed in the last ESMO guidelines for metastatic colorectal cancer. This aggressive approach needs to be in the context of a randomized clinical trial. The authors need to discuss this. To this reviewer knowledge, at the present time there is only a randomized trial (PRODIGE trial in France) being conducted testing this strategy. A similar trial was close due to low".*

This has now been done and alterations made have been highlighted and can be found on page 21 of the manuscript and the abstract on page 4.

## **Comments by reviewer 2:**

1. *"The authors described many limitations of this study in discussion, such as time dependent bias, small case series, treatment heterogeneity, and selection of patients in page 23. In addition, I find other limitation in page 24 and 25. The half of discussion shows limitations of this study. Please summarize the limitations in one or two pages."*

We apologise for this and have now restricted our limitations section purely to one section found in pages 19-20 which is highlighted. We are grateful to reviewer 2 for pointing this out.

2. *"Please describe the comparison of survival between the intraperitoneal chemotherapy and recent molecular targeted therapy".*

This has now been done and is highlighted and reported on page 21. None of the studies included in this review described the use of any molecular targeted therapies in the treatment of peritoneal metastases from colorectal cancer.