

Manuscript 18855**Title: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in gastric cancer****Comments: Reviewer 3017854**

In this original manuscript Ramakrishnan and colleagues compiled and reviewed HIPEC in patients with gastric cancer and peritoneal carcinomatosis (GCPC). This review manuscript nicely captures the overview and current state of HIPEC for patients with GCPC. The manuscript discusses the mechanism of peritoneal carcinomatosis and then focuses on the risks and benefits of HIPEC in the neoadjuvant, adjuvant and palliative settings. In each setting, the authors discuss and compile nice tables for trials that specific to each clinical setting. The authors conclude that while HIPEC is not the standard of care, the “role of CRS with HIPEC in GC with macroscopic PC is still evolving and needs to be addressed in large multi-institutional randomised trials.” The article is well organized and well written, and moderately relevant to the overall journal readership. The in-depth content reflects the authors’ expertise in the field. There is significant variability in the quality of published PC trials and the authors should address this in a more formal method. I think the importance of this review would be improved if the authors assigned a grading criteria to the quality of the evidence supporting the described clinical situations. A general A, B, C with a brief description in the beginning of the review would be helpful to the reader. I also feel the emerging bi-directional evidence involving systemic and intraperitoneal chemotherapy should be discussed in more detail. I would expand some on the role of docetaxel and less on the older studies, but this is not required for publication. The review dose seem to paint HIPEC in a positive light, and the potential complications and adverse effects could be expanded upon. Overall I feel this is acceptable for publication.

Response:

1. We thank the reviewers for their comments and suggestions. We agree that there is variability of the published trials. We have added a statement to this effect in the revised manuscript. However, since this is not a meta-analysis, we have not assessed the quality of trials using a quality assessment scale like the Jadad score. Instead, we have made it clear in the text regarding the nature of the study. Further, we have specifically mentioned the type of study (RCT or prospective etc.) in the Table 1 and 3 in a separate column which will give the reader a good measure of the level of evidence discussed.
2. We have already devoted 3 paragraphs to the bi-directional chemotherapy and discussed in detail the technique and results of this method (pages 35-36)
3. The complications of HIPEC have been discussed in a paragraph in page 11. We have also included the incidence of the important complications in 4 columns in Table 2.

Comments: Reviewer 502831

The authors reported about the cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in gastric cancer. I think this article is usefulness of realizing the treatment of peritoneal metastasis from gastric cancer. However, there is lack of recent treatments of peritoneal metastasis from gastric cancer. Moreover, adverse effects of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy were very severe, and these treatments have a lot of costs and the ethical problems. So, these treatments are able to be performed in limited a few

institutions and for limited a few patients. The authors listed hyperthermic intraperitoneal chemotherapy for peritoneal metastasis from gastric cancer. But the used drugs were conventional anticancer drugs such as MMC, CDDP, 5-FU and etoposide. I think these drugs may be not effective for peritoneal metastasis. Recently effectiveness for peritoneal metastasis from gastric cancer of combination therapy with docetaxel of intraperitoneal and intravenous administration has been reported. This treatment is thought to be safe and effective. The authors should described usefulness of intraperitoneal administration of Doc and introduced several clinical study about intraperitoneal and intravenous administration therapy with Doc.

Response:

1. We agree that this procedure is a specialised procedure and is performed in few centres and benefits few patients. We have therefore discussed in great detail about the criteria for selecting patients who are likely to benefit from it.
2. Although docetaxel is a promising drug for intraperitoneal use, there is a paucity of evidence from the literature to support the use of docetaxel for HIPEC in gastric cancer. We were not able to identify any study that has used docetaxel alone, instead it has been combined with other agents like oxaliplatin or cisplatin in few small studies. We have added relevant literature regarding use of docetaxel intraperitoneally.

Comments: Reviewer 58401

Congratulations for the quality of the work-liberatocaboclo@gmail.com