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Response Letter
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**Gastric peritoneal carcinomatosis – a retrospective review**

We thank the journal editors for considering our manuscript for revision and all three reviewers for their insightful and constructive comments. Please find our responses to the reviewers' comments as follows:

**Reviewer No. 113940**

*A drawback of this study is that the grade of peritoneal metastasis was not classified. Generally, it is classified as P1, P2 or P3 according to the recommendations of the Japanese Research Society for Gastric Cancer. The classification is useful for predicting patient outcomes and tailoring treatment. The reason for not classifying peritoneal metastasis should be described in the Discussion. Alternatively, comparing the outcomes of synchronous peritoneal carcinomatosis that was found on CT (probably not including P1) and those of the lesion detected by a laparoscopy (probably including P1) would be informative.*

The Japanese classification of gastric cancer classified peritoneal metastases as P1, P2 or P3 in its first edition. Due to subsequent studies demonstrating a lack of prognostic value in this classification system, the Japanese classification of gastric cancer modified the peritoneal metastases classification to P0 or P1 to indicate absence or presence of peritoneal metastases in the second and third editions. Further, due to the retrospective nature of the study, the reporting of the degree of peritoneal metastases either on pre-operative imaging or intraoperative findings was not standardized between physicians and over time. In view of these reasons, we did not opt to report the "grade of peritoneal metastasis" as the reviewer pointed out.

The outcomes when compared between synchronous peritoneal metastases diagnosed on CT scan vs those diagnosed intra-operatively were not significantly different. Further, as the primary goal of the study was to examine how patients with gastric peritoneal carcinomatosis fared with chemotherapy, attempting to distinguish any differences in outcomes between different modalities of diagnosis of peritoneal metastasis would be tangential and potential convolutes the primary research question.

**Reviewer No. 204529**

*The authors have written a review of a single institution experience with patients with gastric cancer and carcinomatosis to give some idea of the treatment history of such patients treated over a 4-5 year period. Some unsurprising observations are made, including patients with treatment with supportive care alone only living 1-2 months. The authors play up to strongly that peritoneal carcinomatosis may represent treatable "local regional" disease, however, regional therapy for these patients remains highly controversial. Outcomes from patient series likely reflect a high degree of patient selection, and outcomes may be more reflective of tumor biology than the actual impact of regional therapy on these patients. The "shift in paradigm" for these patients is hardly universally accepted. However, some have embraced regional therapies without carefully conducted, randomized clinical trials. More information should be provided in the abstract, and in the results, survival curves showing marginal and often not surprising survival differences should be deleted. Does their definition include patients with positive cytology found at laparoscopy without gross visible carcinomatosis? The authors also talk about "completing" chemotherapy, is this ever really the case in metastatic gastric cancer? Although the U.K approach is to deliver 6 months of chemotherapy and then observe patients, others globally continue chemotherapy until disease progression, and given that the median PFS for most patients is 4-5 months ongoing*

*chemotherapy is usually the situation. The discussion is repetitive and editorializing and needs to be truncated. Specific comments are outlined below: Abstract: Should contain more information about therapy delivered and patient characteristics. Poor outcome in patients requiring hospitalizations is less a reflection just of peritoneal carcinomatosis but the failure of our currently available modestly active systemic chemotherapy. To date there are no compelling randomized trial data indicating that regional chemotherapy will improve outcome in these patients, this statement should be deleted or rephrased to indicate that investigational use of regional therapies is warranted and requires validation. Introduction: Gastric cancer is no longer the second leading cause of cancer related death, this misstatement needs correction. It is already recognized from prognostic factor series that peritoneal disease is an independent, poor prognostic factor; the authors should acknowledge this literature. The case for intraperitoneal therapy to be studied is supported by the authors report, but its actual clinical use is not. Methodology: Did the authors capture the issue of visible carcinomatosis, versus cytology only documentation? Discussion: The authors imply that regional chemotherapy is now a therapy standard for peritoneal carcinomatosis. This is hardly the case given the absence of controlled clinical trials. Retrospective series subject to patient selection bias should not be cited as evidence of benefit for a therapeutic approach.*

The “shift in paradigm” which the reviewer contends with has been changed to “a growing interest” in the manuscript discussion section.

We have removed the previous “Figure 2: Overall survival of patients with isolated peritoneal metastasis vs patients with peritoneal and concomitant distant sites of metastasis” which featured a survival curve showing non-statistically significant difference.

Our patients who “completed” their course of chemotherapy were patients whose disease were controlled and went into remission with systemic chemotherapy, with a clinical decision to continue surveillance thereafter. This is also already stated in our results section – “Eventually, only 14 (8.2%) patients completed their courses of chemotherapy with subsequent close clinical surveillance.” As the reviewer rightly pointed out, such patients are few and far between for metastatic gastric cancer which is consistent with our results.

We have added some details on treatment to our abstract – “Choice of first-line regime was in accordance with the National Comprehensive Cancer Network Guidelines for Gastric Cancer Treatment.” Patient details included in the abstract were kept brief and concise to allow for more focus on the description of the results relevant to our primary study objectives within the abstract.

We’ve modified our statement in the conclusion portion of the abstract to incorporate the reviewer’s suggestion of phrasing it as “As such, investigational use of regional therapies is warranted and required validation in patients with isolated PC to maximize their survival outcomes in the long run.”

We have corrected the introduction to indicate that gastric cancer is the third leading cancer related cause of death worldwide rather than second. We have also added the recognition of peritoneal metastasis as a recognized independent predictor of poor outcome in gastric cancer.

We have changed the introduction as well to indicate that we are supporting further “study” into the use of regional therapies rather than the “use” of it directly.

We did not include patients with solely positive peritoneal cytology. We have included this clarification of definition in our manuscript “Methodology” section.

We have modified the phrasing of key sentences in the discussion and our conclusion to highlight the point that regional therapies remain studied at the moment and are not the standard therapy across all peritoneal carcinomatoses.

**Reviewer No. 3551392**

*The authors present a retrospective study of a cohort of patients with gastric cancer and peritoneal metastases treated in a single oncology center. The rationale for the study is important as the prognosis remains poor in this group of patients. The study derives a lot of clinical data describing patients' baseline characteristics and their course during palliative therapy. The results are consistent with those presented in previous studies. However, there are some remarks that need to be verified before the publication. 1. Epidemiological data mentioned in the introduction are outdated. For latest data, please check: http://globocan.iarc.fr/old/FactSheets/cancers/stomach-new.asp 2. Please, provide the definition of follow-up and its method of calculation. 3. Please, provide confidence intervals for median OS in each subgroup of patients. 4. Disagree with the sentence: 'This is consistent with the idea of isolated peritoneal carcinomatosis as a loco-regional disease extension rather than a true systemic dissemination of metastatic disease, which further lends support to the cause of aggressive loco-regional treatment with CRS and HIPEC in at least selected cases to maximize survival outcomes.' Firstly, this study is not constructed to bring an evidence for the thesis. Secondly, there is no consensus if peritoneal metastases appear as loco-regional extension or systemic dissemination, and definitely no validated data that support the use of loco-regional treatment in a routine practice. 5. Strongly disagree with the sentence: 'This is consistent with our finding of significantly improved overall survival in patients who initiated systemic chemotherapy compared to those who received best supportive care upfront.' This conclusion is wrong in terms of retrospective study as selection-bias occurs. Patients treated with best supportive care could have worse outcomes because of worse baseline parameters that disqualified them from chemotherapy when compared to baseline parameters of patients that received chemotherapy. The positive effect of chemotherapy could be proven only when both groups had the same baseline characteristics within known prognostic factors and only one group would receive chemotherapy.*

1. We have updated the epidemiological data and cited it in our references accordingly

2. The follow-up and the fact that chemotherapy or other interventions were administered accordingly during follow-up have already been described in our methodology section. Follow-up is simply calculated as per any other studies, but as per the reviewer's request, we have added "Follow-up duration of each patient is calculated in months beginning from initial diagnosis till the last follow-up or death at the point of data collection." to our methodology section.

3.

4. We have rephrased the sentence to read "This is consistent with proposed theories of isolated peritoneal carcinomatosis as a loco-regional disease extension rather than a true systemic dissemination of metastatic disease, which further lends support to the investigational use of aggressive loco-regional treatment with CRS and HIPEC in at least selected cases to maximize survival outcomes."

5. We have removed this line in contention.

We hope you will consider the manuscript favorably and look forward to hearing from the journal. Thank you.

Yours sincerely,

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