REPSONSE LETTER

Dr. Fang-Fang Ji

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Manuscript Title: Approach to Pseudomyxoma Peritonei

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Dear Dr. Fang-Fang Ji,

We thank you and the reviewers for their interest in our work and for helpful comments that will greatly improve the manuscript and we have tried to do our best to respond to the points raised. The reviewers have brought forward some good points and we appreciate the opportunity to address their concerns.

As indicated below, we have checked all the general and specific comments and provided either a revision or explanation. We have broken down the reviewer's comments by each reviewer.

Reviewer 1: 0244558

Comment:

This is a very well written review on a specific topic such a pseudomyxoma peritonei. Overall it reads well and is well structured. One main comment is the slight discrepancy between the pathogenesis and the histology as in the latter it is postulated that a benign origin is possible and indeed more frequent whereas in the pathogenesis the authors refer to the same sequence observed in the adenocarcinoma of the large intestine. This should be clarified as it is not clear.

Reply:

Thank you for the suggestion. It has been considered. The reviewer is correct, the pathological process of pseudomyxoma is that of neoplastic transformation of appendiceal goblet cells, not an adenocarcinoma per se. The authors were trying to draw a parallel with colon cancer for easier understanding for the readers. This was however unclear and therefore we have removed that analogy.

Change made:

" The pathological process of PMP starts similar to most primary tumours of the alimentary tract(1). The adenocarcinoma sequence is found to occur in the appendix, as it does in the colon.

Neoplastic transformation of the goblet cells results in the formation of a primary mucinous tumor."

Now is,

"The pathological process of PMP starts similar to most primary tumours of the alimentary tract(1). Neoplastic transformation of the goblet cells results in the formation of a primary mucinous tumor."

Reviewer #2: 00043396

Comment:

A very well written and concise review of the topic.

Reply:

Thank you for your comment.

Reviewer #3: 02463725

Comment:

This is a review article regarding pesudomyxoma peritonei. The article was well-written, and summarized the disease comprehensibly, although the data and articles regarding this disease are limited. 1) I do not think that the incidence of the disease (1-2 out of a million) is correctly estimated. The number appears to be too low. 2) At the section of histology, the specific cases with DPAM, PMCA, and PMCA-I as well as the cases with high-grade and low-grade should be given, with presenting CT images and/or histologic figures. 3) The treatment methods and prognosis after recurrence of surgery with chemotherapy should be provided.

Reply:

Thank you for the suggestions, they have been considered and appropriate changes have been made. We will address them in order.

1.

Based on our literature review it was found that the exact incidence of the disease is unknown. It is best estimated to be 1-2 or 1-3 million, per year. We will make a clarification in the paper to highlight that is an incidence per year.

Change made:

"Incidence of the disease is best estimated at 1-2 out of a million."

Now is,

"Exact incidence of the disease is unknown but has been estimated at 1-3 out of a million, per year."

2.

This is a great suggestion, we will be adding CT imaging and Histological figures to the paper.

3.

Thank you for this suggestion, we had not considered discussing recurrence and prognosis after recurrence. We have added a short discussion on recurrence management.

Change made:

"Despite these outcomes after CRS and HIPEC, there is significant recurrence of the disease. Yan et al. found recurrence to be as high as 28%, the majority of these patients underwent repeat surgery (21). Lore et al, conducted a retrospective analysis on 512 patients undergoing CRS with HIPEC for PMP, they found that 26.4% (137/512) developed recurrence and 25.5% (35/137) underwent repeat surgery. Complete tumour removal was achieved in 20/35 (57.1%). They found that there was no significant difference in early post-operative complications in comparison to primary CRS surgery. The 5-year OS in the 375 without recurrence was found to be 90.9%, the 35 that had repeat CRS had a 5 year OS of 79% (5). The literature suggests that if recurrence does occur, a second CRS procedure is feasible, however, the data is limited due to small sample sizes. Continued data collection is needed to draw stronger conclusions on how to approach a patient with recurrence."

Reviewer #4: 00053888

Comment:

I think that this is a useful and timely review of the presentation, diagnosis and treatment options for this rare tumour. I think that the manuscript is about the correct length, but I think the headings and sub headings need a little work. The authors seem to have started with a more conventional introduction, methods, etc approach and then stalled and reverted to a series of sub headings that do not follow ant logical pattern. A short introduction and discussion regarding the literature search is reasonable but the authors would then be better moving to a more conventional approach of presentation, demographics, diagnosis, treatment and outcome.

There are also a number of typographical errors and the manuscript lacks some figures such as CT, histology, operative picture. Figure 1 is pointless and table 1 is just repetition of what is in the text.

Reply:

Thank you for the feedback, we have taken into consideration your suggestions. In terms of the headings and subheadings we have changed them to a more conventional approach but maintained some aspects that we found to be necessary for a literature review of a disease.

1. Headings and Subheadings:
Changes made:

- Introduction heading will be left as is.
- "Methods" heading is removed, replaced with "Literature Search Strategy," as this is a literature review.
- We removed the "Terminology" subheading and its contents.
- "Pathogenesis" will be kept as this is vital to the understanding of the disease process, natural history.
- "Clinical Presentation" will be kept as is.
- We prefer the heading "Disease Burden" to "Demographics" as there is limited data on demographics. The data is limited to incidence alone.
- We have replaced "Diagnostic Methods" with "Diagnosis"
    - Removed the subheadings "radiological imaging" and "tumour markers"
- Under the heading "Treatment" we have removed all subheadings and created a new heading "Treatment and Outcome."

2. Typographical errors
Changes made:

- We have added CT images, histology figures, and an operative picture.
- We have removed figure 1 and table 1.
- Figures 1, 2, 3 and 4 have been added.

We hope to have addressed all of the concerns of the reviewers. Should there be further revisions needed, we are open to making changes.

Regards,

Syed Ali Rizvi, Wajahat Syed, Ravi Shergill