Peer Review File

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Reviewer A:

Comment 1: How to calculate a PCI and documenting distribution the peritoneal disease should be emphasized.

Reply 1: A diagram that facilitates the PCI determination was added to the manuscript. Reference 15 was also added to the manuscript. Instructions as to how to use the PCI and the threshold for including patients in CRS and HIPEC protocols was presented.

Changes in the text: Changes were made on page 4.

Comment 2: Unresectable metastases (such as portal encasement) would change the approach and should be discussed.

Reply 2: The role of the completeness of cytoreduction score in evaluating these patients was discussed.

Changes in the text: There was an addition to the text on page 4.

Comment 3: Peritoneal disease is often discovered with hepatic metastases; how would the authors suggest handling this eventuality.

Reply 3: The impact of finding hepatic metastases and the extent of liver metastases that are discovered in this clinical setting were discussed. References 17 and 18 were added to document the additional information.

Changes in the text: Changes were made on page 5.

Comment 4: Although synchronous HIPEC with unexpected disease is theoretically possible the reality is that very few centers will be able to add the several hours to a case needed with the expertise immediately available to accomplish this and this should be added to the discussion.

Reply 4: The requirements for adding CRS plus HIPEC were presented. The authors agree with the reviewer that few centers will be able to perform an unscheduled CRS and HIPEC.

Changes in the text: This information was added to the text on page 6, paragraphs 2 and 3.

Comment 5: The PRODIGE 7 trial should be cited and its implication for complete resection of all peritoneal metastases (potentially without HIPEC) particularly for low PCI easily resected disease must be discussed.

Reply 5: Data regarding this important issue was added to the manuscript (Reference 28). We agree with the reviewer that patients with low PCI may be considered for definitive CRS in the absence of HIPEC.

Changes in the text: This was added to the manuscript on page 7.

Comment 6: Many patients with obstructing lesions may benefit from either bypass or resection and primary anastomosis in the acute setting, as many such patients will not end up undergoing CRS +/- HIPEC and would have a poorer quality of life if routinely treated with a stoma in this setting. Some discussion of this would be beneficial.

Reply 6: These options were mentioned in an added paragraph on page 11. The literature does not support bypass or resection and primary anastomosis. Our manuscript would suggest that this treatment will be used in a highly select group of patients.

Changes in the text: This information was added to the manuscript on page 11, paragraph 2.

Comment 7: When finding peritoneal disease in the setting of a perforation, a biopsy of the peritoneal disease is warranted to help define future care.

Reply 7: We agree with the reviewer.

Changes in the text: A sentence was added on page 13, paragraph 3 to emphasize that peritoneal disease must be biopsied.

Comment 8: Documenting the PCI (or at least a description of the peritoneal disease) should be clearly suggested as being a key part of the operative report.

Changes in the text: This recommendation was added to the manuscript on page 4.

Reviewer B:

Comment: The major criticism of this manuscript pertains to the focus on neoadjuvant treatment (NAT) within your proposed treatment algorithm. The recommendations in this manuscript include the administration of NAT for patients in all treatment arms, with the exception of those undergoing surgery at a centre where CRS/HIPEC is available. At present, there is no convincing evidence that supports the utility of NAT in the subset of patients with colorectal cancer (CRC) and peritoneal metastases (PM). As your manuscript itself recognises (Page 4, lines 111 - 123), current evidence on the use of NAT in CRC patients is derived some studies that have specifically excluded patients with PM. NAT is not yet standard of yet in this subset of patients, and at best, preliminary Phase II results from the study most likely to add weight to your hypothesis (CAIRO6) are equivocal. For example, your treatment algorithm proposes that patients who are found to have PM at a centre without CRS/HIPEC should have a limited resection, then proceed to NAT, and then finally to definitive CRS/HIPEC. This is in contrast to currently established pathways elsewhere where patients may be referred straight to a CRS/HIPEC centre

following initial unexpected diagnosis of CRC and PM. More justification is needed with regards to the key role that NAT plays in this manuscript. This is a key component of your treatment algorithm, and a more substantial, evidence-based rationale for its utility is necessary here.

Reply: The reviewer's comments are well taken. However, the authors are convinced that these peritoneal metastases patients are a group at very high risk for surgical treatment failure. The use of a short course of neoadjuvant chemotherapy has not been shown to do harm. A group of poor responder patients with unsalvageable progression has not been reported. The use of neoadjuvant chemotherapy may help improve the outcome of this group of patients but more data is needed. Our response to the reviewer is positive. Nevertheless, our algorithm for treatment was not changed because of our conviction that neoadjuvant treatment is of help to the patients with colon cancer at high risk for treatment failure. No additional publications were available for us to support this decision.

Changes in the text: A paragraph was added on pages 9 and 10 to discuss the reviewer's comments and respond with our opinions regarding neoadjuvant chemotherapy.

Comment 1: There is an insufficient focus on the patient, technical and institutional factors which certainly impact on the decision whether to proceed with emergency "unplanned" CRS/HIPEC. The threshold to proceed with immediate CRS/HIPEC is likely to be higher than that necessary to proceed with elective CRS/HIPEC. A simple breakdown of proposed inclusion and exclusion criteria for emergency CRS/HIPEC would be a helpful adjunct.

Reply 1: An added paragraph to discuss factors which impact on the decision to proceed with an unscheduled CRS and HIPEC was added to the manuscript. No specific inclusion or exclusion criteria could be offered.

Changes in the text: Paragraph added on page 6, paragraphs 2 and 3 and page 7, paragraph 2.

Comment 2: Is there any comparison of non-oncological complication profile between immediate CRS/HIPEC and delayed CRS/HIPEC. I would hypothesise that this would be lower in the delayed group due to the ability to pre-operatively optimise these patients but inclusion of any data pertaining to this would be helpful.

Reply 2: No data that we know of is available to answer this important question.

Changes in the text: The unanswered question was addressed on page 6, paragraph 3.

Comment 3: Page 2, lines 60/61 allude to an impact of operative approach (laparoscopic, robotic, or open) on the decision to perform CRS/HIPEC. Could this be expanded upon further.

Reply 3: The impact of minimally invasive versus open surgery on the decision-making process when the primary cancer is not removed was discussed.

Changes in the text: This discussion was added to the manuscript on page 8, paragraph 2.

Comment 4: What is the rationale for adjuvant chemotherapy in the populace that has already received NAT specifically in the context of CRC?

Reply 4: A discussion of the utility of neoadjuvant versus adjuvant chemotherapy was added

Changes in the text: Changes made on page 9 and 10.

Comment 5: A brief overview of the logistics entailed in preparing for "emergency" or "unexpected" CRS/HIPEC may be of interest.

Reply comment 5: A discussion of the logistics for unplanned CRS plus HIPEC was added to the manuscript.

Changes in the text: Added paragraph on page 6, paragraphs 2 and 3, and page 7, paragraph 2.