Ruo-Yu Ma

Director

Science Editor Development Department

Baishideng Publishing Group

April 14th, 2020

Dear Ruo-Yu Ma,

We would like to thank you for your reply to the manuscript, which we submitted under the title: **'Comparison of different HIPEC-Regimes and prognostic factors for treatment of peritoneal metastasized colorectal cancer'**

We are very pleased that you and the reviewers found the topic of the manuscript interesting.

We have carefully read all of the comments and suggestions made by the reviewers. All suggestions have now been taken into account and corresponding changes made to the manuscript. All changes or revisions to the contents are **bold** in the revised manuscript.

First, we want to thank the reviewers for their very helpful advice. We think that these comments have improved the quality of our revised manuscript. Listed below are our specific answers to the reviewer's comments:

REVIEWER 1:

1. *In this manuscript, Spiegelberg et al. conducted a retrospective cohort study to evaluate the therapeutic efficiency of cytoreductive surgery with different heated intraperitoneal chemotherapy (HIPEC) regimens in patients with colorectal cancer, comparing MMC HIPEC vs. oxaliplatin HIPEC. […] With these results, authors deemed that further studies comparing HIPEC regimes would improve evidence-based decision-making. This is a carefully done study and the findings are of considerable interest.*

   We are very pleased that found the topic of the manuscript interesting and enjoyed reading it. We hope we can answer your questions adequately.

2. *As the authors said in the Introduction section, HIPEC with MMC has been merely used as salvage treatment since HIPEC with oxaliplatin became standard systemic treatment in*

colorectal cancer with peritoneal metastasis. Although there was no prospective study that compared these two HIPEC regimens, reviewers have doubts that these two regimens are clinically comparable to efficiency. More evidence is needed to support the choices of authors.

The HIPEC regimens was chosen on basis of the current available data. Starting 2007 till 2014 MMC was used, and then changed to Oxaliplatin until 2018 with increasing evidence for oxaliplatin as standard systemic treatment in colorectal cancer with peritoneal metastasis. Analogous to PRODIGE7 trial HIPECs since 2018 were conducted with MMC. We describe our decision making in the methods section.

(Page 7, lines 16-19)

3. *The inclusion and exclusion criteria of the cohort are vague. For example, reviewers are unaware of which type of cancer is included or excluded. Clear and detailed criteria need the listing to make results convincible.*

Our inclusion Criteria were patients with peritoneal carcinomatosis of colorectal origin who underwent CRS and HIPEC between January 2007 and March 2019 at the medical Center of the University Freiburg (MCUF). As our focus was to evaluate differences in HIPEC regimens we included patients who underwent palliative or cytoreductive surgery and HIPEC. Patients with appendicial tumours / Pseudomyxoma peritonei and Peritoneal carcinomatosis of other origin (non colorectal) were excluded as well as patients who were planned for HIPEC, but have not received HIPEC treatment due to surgeons intraoperative decision (e.g. no CC-0 level could be obtained due to irresectable perioneal carcinomatosis.)

The Inclusion and Exclusion criteria are listed in the methods section.

(Page 7, lines 5-11)

4. *The authors did not mention the loss to follow-up, which is fundamental to this research. A patient selection scheme should be provided in the paper to clarify the detailed methods to define the two cohorts.*

We agree that a loss to follow-up rate has to be included in this retrospective cohort study. We have a LTFU rate of 3.9 % (4 patients). All of them were treated with MMC-HIPEC. We have added a small paragraph in the result section.

(Page 11, line 16-17)

Patient selection was conducted in an interdisciplinary setting with the oncolcogy department. All patients were discussed in our interdisciplinary cancer conference and decision for cytoreductive Surgery with HIPEC was made, if a complete resection seemed achievable. Since 2007 all of these patients were included in our retrospective analysis if HIPEC was performed. Whether patients were treated with MMC or oxaliplatin HIPEC was dependent on the treatment period. HIPEC regimens were chosen regarding current available data. Starting 2007 till 2014 MMC was used, and then changed to Oxaliplatin until 2018 with increasing evidence for oxaliplatin as standard systemic treatment in colorectal cancer with peritoneal metastasis. Analogous to PRODIGE7 trial HIPECs since 2018 were conducted with MMC.

(Page 7, lines 16-19 and 26-28)

5. *There is a bias between the baselines of the two cohorts. However, the authors failed to prove whether the bias influenced the results, making them controversial, and it is confusing to determine the actual cause of a similar median overall survival (OS).*

   We perfectly agree on your statement regarding the baseline difference between the two cohorts. Concerning the retrospective data it is not possible to determine whether the similar median overall survival is due to different baseline characteristics or different therapy response. As we have written in our cohort, MMC group had a trend towards a higher PCI-scoring and a smaller number of CC-0 resections, which could possibly be responsible for the observed trend towards a prolonged survival in the Oxaliplatin group as well as differences in systemic preoperative treatments regarding multi-agent and targeted systemic therapy and surgical approach. Due to the retrospective design of our study there is a lack of information regarding survival outcome factors. As the two collectives differed at baseline with MMC group having a trend towards higher PCI-scoring and a smaller number of CC-0 resections, it is not possible to show whether the statistical trend towards the oxaliplatin/5-FU group is caused by baseline characteristics or HIPEC efficiency. A prospective comparative study would be of high interest.

   We acknowledge this problem in the discussion section.

   (Page 13, lines 25-32)

6. *Different types of cancer response to chemotherapy differently. Colorectal cancer (CRC) includes adenocarcinoma, adenosquamous carcinoma, squamous carcinoma, and so on. It is necessary to include patients with the same type of cancer into cohorts. That way, the selection bias could be reduced.*

We agree that different types of histopathological carcinoma types could influence outcome after chemotherapy. In our cohorts 21% of tumors (18% in the MMC group and 22% in the Oxaliplatin group) were mucinous carcinoma. Regarding univariate analysis we found no survival benefits for mucinous carcinoma vs. adenocarcinoma. Our cohort contains no patients with adenosquamous or squamous carcinoma. It would have been of great interest to analysis the histopathological and oncogenetic factors like microsatellite instability and RAS/RAF status, but not enough data was available from our records.

We acknowledge this problem in the discussion section.

(Page 15, lines 14-19)

7. Minor issues:

- *Page 6 Line 4: It would be better if the paragraph is combined with the previous paragraph.*
- *Page 18: The second paragraph should be combined with the previous one. It would be better if the third and fourth paragraphs were combined.*
- *The authors have mentioned PCI-score several times, but there is no explanation for its meaning. A rating scale attached would be lucid.*
- *There is an absence of a description of Figures1 & 2 in the Result section.*
- *The authors mentioned 'PRODIGE 7' three times in the manuscript, but the reference is missing.*

We thank you for this comment. We have now combined the paragraphs as suggested, and added a description to Figure 1 and 2 in the result section.

(Page 6, line 6-7; Page 13, line 7-8 and Page 21/22)

We agree that there is no explanation for the PCI score in our manuscript. According to Sugarbakers original work the Peritoneal Cancer Index (PCI) system divides the abdomen and the pelvis into 13 regions. The lesion size of the largest sizes of the largest implants is scored (0 through 3) in each abdominopelvic region. They can be summated as a numerical score, which ranges from 1 to 39. (Glehen O, Kwiatkowski F, Sugarbaker PH, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol*. 2004;22:3284–92.) We added a rating scale description to out manuscript.

(Page 8, line 18-22)

As the 'PRODIGE 7' trial is the first prospective trial to compare CRS + HIPEC vs. CRS, it is one of the most important references for current HIPEC trials. The reference is missing because the study results are still not published, but we have now a paper discussing the results.

(Page 14, line 1-3)

REVIEWER 2:

1. *INTRODUCTION - Multimodal treatment does not consist of debulking + HIPEC but of cytoreductive surgery + HIPEC. - It should be emphasized that a widely used protocol provides for the association of mmc with cisplatin (example of references: Macrì A, Arcoraci V, et al. Short-term outcome of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy used as treatment of colo-rectal carcinomatosis: a multicentric study. Updates Surg. 2019 Nov 15. doi: 10.1007/s13304-019-00691-8. Macrì A, Saladino E, et al. Peritoneal carcinomatosis of colorectal origin. World J Gastrointest Oncol. 2010 Feb 15;2(2):98-101. doi: 10.4251/wjgo.v2.i2.98.)*

   We thank you for your remark and added a reference describing the combination of MMC and cisplatin. At the university hospital of Freiburg CRC HIPECS were performed with MMC as monotherapy.

   (Page 5, line 29-31, page 6, line 1-2)

2. *In light of current knowledge it cannot yet be stated that "Upfront cytoreductive surgery with HIPEC (CRS-HIPEC) is nowadays the standard"*

   The results of the prodige study show very good results for selected patients that undergo CRS. The value of the additional HIPEC remains unclear. However there is little doubt that CRS is superior to palliative chemotherapy for suitable patients and therefore can be considered the standard of care for eligible patients. We have elaborated in the introduction.

   (Page 6, lines 3-5)

3. *PATIENTS AND METHODS - Since patients treated with mmc or OXA refer to two different and consecutive periods, the impact of the learning curve must be assessed.* We agree that the learning curve could have an impact on overall survival. Different surgeons performed HIPECs at the university hospital of freiburg. Therefore an individual learning curve can't be

assessed. Nevertheless the learning curve of the surgical department could influence postoperative outcome. We therefore added a small paragraph in our discussion.

(Page 14, lines 6-9)

4. *Patients treated for palliative purposes cannot be associated with those treated radically. - The authors must analyze the patients who died within 90 days with particular reference to the various factors potentially responsible.*

We agree that palliative resections should not be associated with operations performed in a curative intend regarding the analysis of overall survival. However, in this study, the main focus was safety and efficacy of the HIPEC protocol and the percentage of palliative resections were low and comparable in both groups, therefore we have decided to include them in the analysis. From the 102 patients analyzed, 11 died during the first 90 days after Surgery but all after hospital discharge and therefore mainly for oncological or other medical causes. We have elaborated in the results section.

(Page 12, lines 1-2)

5. *Was multivariate analysis performed for morbidity assessment?*

We thank you for this comment. As mentioned by the reviewers, there has been several studies trying to identify risk factors for postoperative morbidity after CRS and HIPEC published in the literature.

Due to the relatively small number of patients in this study and the heterogenous extend of the surgical approach, a risk factor analysis and multivariate analysis seemed to be of little value and therefore has been omitted.

6. *TAB. 1 - Authors should separate CC1 patients from CC2-3 patients.*

We have changed our table accordingly.

(Table 1)

7. *TAB. 2 - Enter the mortality data.*

We have changed our table accordingly.

(Table 2)

8. *TAB. 3 - Carry out a separate and comparative analysis between patients treated with MMC and those treated with OXA.*

   The separate Analysis of the two groups regarding factors predicting overall survival shows very similar results. Due to the small number of patients significance level is not reached in many cases. Therefore we have decided to analyse both groups together to identify prognostic factors for improved survival after CRS + HIPEC and to clarify the impact of the HIPEC regimen.

9. *DISCUSSION - Reporting the manuscript on ovarian cancer causes confusion in the reader.*

   We agree and deleted the paragraph on ovarian cancer.

10. *Carry out the analysis of the cases on the basis of the changes made in the text above. treatment for colorectal peritoneal metastases in eligible patients*

    We thank you for this comment and have revised our Discussion accordingly.

    (Pages 13-16)

REVIEWER 3:

1. *This is a retrospective single institution comparison of two different HIPEC regimens for patients undergoing cytoreductive surgery (CRS) for colorectal peritoneal metastases. While the authors found no impact on recurrence/survival, they conclude that oxaliplatin was associated with higher complication rates. HIPEC regimen should have been included (ie forced) into the multivariable model for overall survival especially since there appeared to be a trend on Kaplan Meier analysis.*

   We thank you for this comment and have carried out a separate multivariate analysis for overall survival, adapting the cut-off p-value for inclusion in the model. After Inclusion of HIPEC regimen into the analysis, the prognostic factors identified for improved overall survival remain and the choice of the HIPEC regimen fails to prove significance regarding overall survival at a p-value of 0.144. We have commented on this in the results section.

   (Page 12, lines 26-29)

2. *No multivariable analysis was performed for complications*

   See Reviewer 2 – 5.

3. *A prospective multicenter randomized controlled trial comparing oxaliplatin to MMC for appendiceal cancer patients (Levine et al, JACS 2018) found no difference in overall morbidity but different complication profiles. This should be discussed.*

We agree and have included the paper into the discussion. The major difference between this study and our analysis is the focus and definition of complications. Our study focuses solely on surgical complications in the postoperative phase, while their study aims to analyze hematologic changes postoperatively. Therefore the difference in the results can be explained.

(Page 14, lines 21-26)

4. *Multiple other larger studies have evaluated risk factors for complications among patients undergoing CRS-HIPEC, in general, so this aspect of the study should not be emphasized.*
We thank you for this comment. We omitted a detailed risk factor analysis for postoperative complications due to this reason and focused solely on the impact of the HIPEC regimen. Therefore we have also omitted a multivariate analysis to avoid merely repeating data already published in the literature.

5. *In general, the PRODIGE 7 trial (still not published) is over referenced as the aim of the current study is different.*
We agree that PRODIGE 7 trial is a referenced a few times in our manuscript. As it is the first prospective trial evaluating the benefits of oxaliplatin HIPEC and several findings are concordant to our results we believe that these findings are of central interest for every analysis regarding HIPEC. Nevertheless, we adjusted our manuscript and reduced the references.

(Several Pages)

6. *The abstract has multiple issues: 1) the statement "CRS-HIPEC" greatly improves survival…." Is arguable. 2) aim is not to evaluate "efficiency". 3) PC is not previously defined. 4) "we found no…." as the conclusion is too informal.*
We thank you for your suggestions, we a
dapted our manuscript.

(Page 3, lines 4-6 and 11-12 and 32; Page 4, line 7)

7. *Wording in introduction has multiple issues: 1) "upfront CRS-HIPEC is standard of care" is arguable. 2) "at present there is no prospective…" is not true. See above.*
As mentioned above (Reviewer 2 – 1.), the results of the prodige study show very good results for selected patients that undergo CRS. The value of the additional HIPEC remains unclear.

However there is little doubt that CRS is superior to palliative chemotherapy for suitable patients and therefore can be considered the standard of care for eligible patients.
The Study mentioned above focuses on appendical tumors, therefore it should be stated, that **there is no prospective study that compares these two HIPEC regimens for treatment of peritoneal metastasized colorectal cancer.** We have rephrased the introduction accordingly.

(Page 6, lines 3-6 and 16-19)

8. *I would suggest "regimens" not "regimes" throughout.*

   We agree and adapted our manuscript.

   (Several Pages)

Again, we thank for your reply. We hope that we have adequately responded to reviewers' suggestions and comments and that the attached revised version of our manuscript can be considered for publication.

PD Dr. med. Torben Glatz

Ying Dou

Science Editor

Science Editor Office

Baishideng Publishing Group

May 27th 2020

Dear Ying Dou,

We would like to thank you for your reply to the manuscript, which we submitted under the title ‘Comparison of hyperthermic intraperitoneal chemotherapy regimens for treatment of peritoneal-metastasized colorectal cancer’.

We are very pleased that you and the reviewers found the topic of the manuscript interesting and consider the publication of the revised manuscript.

We carefully read the comments and suggestions made. All changes or revisions to the contents are **bold** in the revised manuscript.

REVIEWER #03372021:

The revised manuscript is ready for publication.

We are very pleased that you found the topic of the revised manuscript interesting and enjoyed reading it.

REVIEWER #04718315:

The manuscript is improved with revisions.

1. The abstract conclusion needs to be revised. Please do not use "we" in a conclusion. The conclusions need to be tempered based on the limitations of the study. For example, "in this single-institution retrospective review of patients undergoing CRS with either oxaliplatin or MMC HIPEC, OS was not different though oxaliplatin was associated with a higher postoperative complication rate".

We perfectly agree on your statement regarding the abstract conclusion and therefore changed the paragraph

(Page 3, lines 8-11)

2. The discussion could be cleaned up. Reorganize concepts, nice clean paragraphs, etc.

We thank you for your comment, we reorganized the paragraphs.

(Various changes, Page 12-15)