Author's response to reviews

Title: Oxaliplatin-based versus irinotecan-based hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with colorectal peritoneal metastasis: a retrospective analysis

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Author's response to reviews: see over
COVER LETTER

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Title: Oxaliplatin-based versus irinotecan-based hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with colorectal peritoneal metastasis: a retrospective analysis
Authors: Gabriel Glockzin, Michael Gerken, Sven A. Lang, Monika Klinkhammer-Schalke, Pompiliu Piso and Hans J. Schlitt

Dear editorial board,

with this cover letter you will find a point-by-point discussion of the reviewers’ comments and our revised manuscript. We hope that the revised version has the potential to be published in BMC Cancer.

Best regards
Gabriel Glockzin

Reviewer: Sherif Abdel-Misih

Major compulsory revisions:

#1 The authors allude to in the abstract and areas of the manuscript that this is an analysis looking at colorectal peritoneal metastases. However, this is not entirely accurate in that the 11/32 patients have appendiceal histology (9 in the oxaliplatin group and 2 in the irinotecan group).

We agree with the reviewer that the appendiceal histology should be mentioned in the abstract. Thus we added the term ‘appendiceal cancer’ to the abstracts and some parts of the revised manuscript.

#2 Granted, sample sizes are often a challenge in most HIPEC studies, I feel that 1/3 of the patients having appendiceal histology is significant given the often more favorable outcomes for appendiceal patients. That being said, though not statistically significant between groups (oxal/iri) with p= 0.139, the 9 patients in the oxaliplatin could certainly play a role in the improved survival trend seen given that figure 2 demonstrates improved survival in the appendiceal patients versus the colorectal. This is a major issue not well discussed and warrants it or exclusion of the appendiceal patients.

We agree with the reviewer that the appendiceal histology might play a role regarding survival after CRS and HIPEC. Nevertheless, only patients with histologically proven PMCA arising from appendiceal adenocarcinoma were included in the present analysis. Moreover, Jimenez et al. recently showed survival rates after CRS/HIPEC in this group of patients that did not differ from the data published for patients with pmCRC. This observation has been discussed in the revised manuscript. At least due to the small number of patients in the present series subgroup analysis does not lead to consistent conclusions. There is anyway no statistical difference regarding survival between the two groups in our series.

Minor essential revisions:

#3 In the abstract, the background does mention the lack of standardization of HIPEC regimens, but does not make mention of the bi-directional approach examined in this study. It is important for the authors to clearly define what is meant by ‘bi-directional’ so that it is understandable to the readers.

The abstract has been revised regarding this point. The term ‘bidirectional’ is now explained in the background section.
To clarify the methods, is it common practice in your institution that due to the retrospective nature of this study, an IRB approval is not required as opposed to a prospective study because this would be unusual in the United States?

As explained in the manuscript an IRB approval is not necessary because the HIPEC regimens used for the treatment of patients included in the current retrospective analysis are ‘standard’ regimens recommended by the German Peritoneal Surface Malignancy Group that and have already been tested and approved regarding their safety. There was no prospective data analysis or experimental drug application. All data has been analyzed retrospectively.

While interesting to understand the perioperative patient management strategies used in your practice, this does not add quality content to the manuscript.

This section has been removed from the revised manuscript.

Reviewer: Ravi Chokshi

Major compulsory revisions:

#1 Review of the literature with updated references.

The discussion has been revised and recently published references have been added to the revised manuscript.

#2 Review of previous mCRC HIPEC treatment doses.

Different oxaliplatin doses have been used for bidirectional HIPEC. However, as mentioned in the manuscript the French standard protocol consists of 460 mg/sqm body surface oxaliplatin. This concentration has been used in most published series. Nevertheless, in a recently published study of oxaliplatin pharmacokinetics during bidirectional HIPEC the oxaliplatin dose has been reduced from 460 mg/sqm body surface to 360 mg/sqm body surface after the first 17 patients due to toxicity. This data has been added to the revised manuscript. The German standard protocol for bidirectional oxaliplatin-based HIPEC consists of 300 mg/sqm oxaliplatin. This protocol is recommended by the German Peritoneal Surface Malignancy Group. Nevertheless, there is no international standardization of the drug concentration. Initial dose finding studies have shown that concentrations higher than 460 mg/sqm oxaliplatin lead to unacceptable toxicity. At a concentration of 600 mg/sqm the haematological toxicity reaches 100%.

#3 Small N from which to draw or infer differences in the absence of statistical support.

We agree with the reviewer that the number of patients treated is too small to draw consistent conclusions. It is beyond question that prospective randomized trials are needed to determine the role of irinotecan in the context of HIPEC. Nevertheless, to our knowledge this is the first series analyzing morbidity, toxicity and survival after irinotecan-based bidirectional HIPEC that might be a second line option for patients with pmCRC that do not qualify for oxaliplatin-based therapy or repeated CRS/HIPEC. Moreover, this preliminary data might be the base for the development and justification of a RCT.

Minor revisions:

#4 Clarification of tables.

The tables have been clarified in the revised manuscript.