

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastrointestinal Oncology

**Manuscript NO:** 51689

**Title:** Comparison of hyperthermic intraperitoneal chemotherapy regimens for treatment of peritoneal-metastasized colorectal cancer

**Reviewer's code:** 03372021

**Position:** Editorial Board

**Academic degree:** PhD

**Professional title:** Professor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Germany

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**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2019-12-31 00:27

**Reviewer performed review:** 2020-01-03 00:55

**Review time:** 3 Days

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## **SPECIFIC COMMENTS TO AUTHORS**

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. The study enrolled 102 patients, in which oxaliplatin and MMC were used in 68 and 34 patients, respectively. Results show that there is no statistic difference in median overall survival between the two groups. However, patients treated with MMC HIPEC show fewer complications (35.3% vs. 66.2%;  $P = 0.003$ ) and shorten ICU stay (4.4 days vs. 7.2 days;  $P = 0.035$ ) compared to oxaliplatin HIPEC. Univariate analysis of survival confirmed that primary tumor factors, nodal positivity and resection margins are of prognostic value, and PCI-score and the completeness of cytoreduction play a key role in peritoneal metastasis. Concerning the multivariate analysis of survival, primary distant metastasis and primary tumor resection status have a great impact on survival and PCI-score regarding peritoneal metastasis. 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. A few minor revisions are list below. Major issues: 1. 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. 2. 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. 3. 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. 4. There is a bias between the baseline 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). 5. 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. Minor issues: 1. Page 6 Line 4: It would be better if the paragraph is combined with the previous paragraph. 2. Page 18: The second paragraph should be combined with the previous one. It would be better if the third and fourth paragraphs were combined. 3. The authors have mentioned PCI-score several times, but there is no explanation for its meaning. A rating scale attached would be lucid. 4. There is an absence of a description of Figures1 & 2 in the Result section. 5. The authors mentioned 'PRODIGE 7' three times in the manuscript, but the reference is missing.

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**Reviewer's code:** 04718315

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Assistant Professor

**Reviewer's Country/Territory:** United States

**Author's Country/Territory:** Germany

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<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## **SPECIFIC COMMENTS TO AUTHORS**

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. The paper has several limitations: 1. 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. 2. No multivariable analysis was performed for complications 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. 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. 5. In general, the PRODIGE 7 trial (still not published) is over referenced as the aim of the current study is different. 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. 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. 8. I would suggest "regimens" not "regimes" throughout

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**Name of journal:** World Journal of Gastrointestinal Oncology

**Manuscript NO:** 51689

**Title:** Comparison of hyperthermic intraperitoneal chemotherapy regimens for treatment of peritoneal-metastasized colorectal cancer

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**Position:** Editorial Board

**Academic degree:** MD

**Professional title:** Full Professor

**Reviewer's Country/Territory:** Italy

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<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## **SPECIFIC COMMENTS TO AUTHORS**

I think the following changes need to be made: 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. - In light of current knowledge it cannot yet be stated that "Upfront cytoreductive surgery with HIPEC (CRS-HIPEC) is nowadays the standard"

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. - 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. - Was multivariate analysis performed for morbidity assessment? TAB. 1 - Authors should separate CC1 patients from CC2-3 patients. TAB. 2 - Enter the mortality data. TAB. 3 - Carry out a separate and comparative analysis between patients treated with MMC and those treated with OXA. DISCUSSION - Reporting the manuscript on ovarian cancer causes confusion in the reader. - 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

## RE-REVIEW REPORT OF REVISED MANUSCRIPT

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**Position:** Editorial Board

**Academic degree:** PhD

**Professional title:** Professor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Germany

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<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input checked="" type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## SPECIFIC COMMENTS TO AUTHORS



The revised manuscript is ready for publication.

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<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## SPECIFIC COMMENTS TO AUTHORS



**Baishideng  
Publishing  
Group**

7041 Koll Center Parkway, Suite  
160, Pleasanton, CA 94566, USA  
**Telephone:** +1-925-399-1568  
**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
**https://**[www.wjgnet.com](http://www.wjgnet.com)

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