

Catanzaro, July, 2022

Dear Editor,

I'm electronically re-submitting our revised manuscript entitled "**HIPEC and CytoReductive Surgery in Colorectal Cancer**" that we would like to have reviewed by Your Journal. The paper has not been previously published and no other submission or publication of the original work has been or will be made. I assure that every author listed meets the qualifications for authorship and had the opportunity to read and comment upon the submitted manuscript. We hope that our article is suitable to be published in your Journal.

Authors' Response

Reviewer 1

We thank the Reviewer for the great consideration of our work.

Following the Reviewer suggestion, we have now revised the manuscript

Reviewer 2

We thank the Reviewer for the great consideration of our work.

Following the Reviewer suggestion, we have now revised the manuscript

Reviewer 3

We thank the Reviewer for the great consideration of our work.

Following the Reviewer suggestion, we have now revised the manuscript

Editor in Chief

Following the Editor in Chief suggestion, we have now revised the manuscript with RCA articles

All new parts in the text are marked in red.

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Answering reviewers for re-review

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Authors' Response

Reviewer 1

We thank the Reviewer for the great consideration of our work.

Reviewer 2

In this paper, the author trying to summarize the most relevant evidences on the use of CRC and to specify the main properties of HIPEC and CytoReductive Surgery (CRS) and their application. Although there are relevant studies and experiments, there is no clear conclusion about which group of patients can benefit from the the bimodal treatment (CRS + HIPEC) against local and advanced CRC. This will also become the direction and focus of future research. The content of the article is relatively smooth, but there are still the following problems: Question1: In page5, the subtitle of this part is "HIPEC and technique", but most of the content is telling the Heat Shock Proteins (HSPs) and related physiological processes and mechanisms, it is suggested that the author consider changing the title of this summary to "HIPEC and physiological mechanism". Question2: About the section headings, "HIPEC and Technique" "HIPEC Technique and Protocols for CRC", the content of the two headings were part of repeat, the author is advised to modify the subtitles. Question3:It is suggested that the author include more updated references in the article. In general, I think this article can be accepted after modification. The final decision should be at the editor's discretion.

We thank the Reviewer for the great consideration of our work.

- 1. Following the Reviewer suggestion, we have now changed subtitle HIPEC and technique with HIPEC and Physiological Mechanism*
- 2. Following the Reviewer suggestion, we have now changed subtitle HIPEC Technique and Protocols for CRC with Protocols of HIPEC for CRC*
- 3. Following the Reviewer suggestion, we have already added the references following RCA system as suggested*

Reviewer 3

I appreciate the hard work the study group invested in this review. Basically, they intended to analyze the results presented in different reviews/systematic reviews on the effects of bimodal therapy (Hyperthermic IntraPERitoneal Chemotherapy and CytoReductive Surgery) on local and advanced CRC. I sincerely hope my remarks will be taken as being constructive and will become useful for a revision. I have listed some suggestions for consideration below: 1. Title - mentions only HIPEC; moreover "HIPEC and Colo-rectal Cancer: from Physiology to Surgery" - appears a bit confusing - Physiology of colo-rectal cancer? Alternatively, why not use "HIPEC and CytoReductive Surgery in colorectal cancer" ? 2. Abstract: The following sentences require revision, as they conflict with each other : " Even if the concept still not very clear and shared, after a careful evaluation of the published data, and after some technical and pathophysiological descriptions, we concluded that it is possible to grow the overall survival, quality of life (QoL) and to reduce the tumor relapse in patients affected by locally advanced (pT4) CRC with peritoneal metastases (PMs). From several studies, it seems that the efficacy of bimodal treatment with an accurate CRS can extend overall survival. Despite some studies, there is no still any straight evidence about the use of combined treatment in patients with CRC." The conclusion is written in the middle while, in the end, there is still uncertainty. Please revise, correct and also improve the quality of the English language. Please make it more concise and clearer. 3. The structure of the manuscript is somehow difficult to be followed. Data could be more logically arranged. A. Introduction mentions many details about HIPEC, in some cancers. However, there are some other paragraphs, describing

HIPEC. Please focus on important aspects and mention only principal data. Also, please describe the abbreviations PM and PMs, before using them. PMs are explained in the Abstract, but not in the main text, only by the end of the Introduction, while they have been used before. B. Material and Methods: The authors wrote “Our revision work has focused the attention on HIPEC, from its first uses to now, looking at principal uses in different tumors like gastric, ovaric and colo-rectal.”. First, this is not a “revision”. Also, “ovaric” is misspelled. Plus, this review should have focused on colorectal cancer. Please also correct “Our study” with “Our review”. C. HIPEC and CRC – these data could be nicely harmonized into Introduction. D. HIPEC and TECHNIQUE – This paragraph is not really about technique. Also, it contains some redundant data. Please revise and summarize. D. HIPEC Technique and Protocols for CRC – Please revise this title as it is a repeat of the previous “HIPEC and Technique” which, in fact, is not much about Technique. This paragraph also presents five studies but not commenting on anything. Please discuss the data. E. CONCLUSION paragraph is not supported by the data presented in the text. Table 1 does not contain explanations. Conclusion should be short and crispy and based on the data presented and commented in the review. Conclusion should not contain references. What do we learn from this review? 4. Figure 2: Please correct the title to “Countries participating in clinical trials” 5. Major revision of the English language is required. 6. Maybe it would be useful to insert a list of abbreviation, given the many abbreviations used in the text. 7. References do not respect the requested format and are not uniformly written. Please correct. 8. Please also insert ORCID for the Authors, according to the requirements of the journal. 9. Also, there are no « Conflict-of-Interest Disclosure Form » and « Copyright License Agreement ». Please insert.

We thank the Reviewer for the great consideration of our work.

- 1. Following the Reviewer suggestion, we have now revised the title with HIPEC and CytoReductive Surgery in Colorectal Cancer*
- 2. Following the Reviewer suggestion, we have now changed the Abstract: “In literature, from several studies, it seems that the efficacy of bimodal treatment with an accurate CRS can extend overall survival. Despite these studies, there are no still any straight guidelines more detailed and scheduled about the use of combined treatment in*

patients with CRC. Even if the concept still not very clear and shared, after a careful evaluation of the published data, and after some technical and pathophysiological descriptions, we concluded that it is possible to grow the overall survival, quality of life (QoL) and to reduce the tumor relapse in patients affected by locally advanced (pT4) CRC with peritoneal metastases (PMs)”

3. *Following the Reviewer suggestion, we have now added Peritoneal Metastases (PMs), focused on important aspects, changed ovaric with ovarian, changed revision and study with review*
4. *Following the Reviewer suggestion, we have now revised and changed the title HIPEC and TECHNIQUE with HIPEC and Physiological Mechanism. Following the Reviewer suggestion, we have now revised and changed the title HIPEC Technique and Protocols for CRC with Protocols of HIPEC for CRC. We have discussed the data of finished protocols with a conclusion. Following the Reviewer suggestion, Conclusion contains no references, we have now changed the title of Figure 2.*
5. *Following the Reviewer suggestion, we have now revised the manuscript with M.D. Thom Douglas (Mother Tongue).*
6. *Following the Reviewer suggestion, we have now added abbreviations.*
7. *Following the Reviewer suggestion, we have now changed references style.*
8. *Following the Reviewer suggestion, we have now added ORCID number*
9. *Following the Reviewer suggestion, we have now added Conflict-of-Interest Disclosure Form and Copyright License Agreement*

All new parts in the text are marked in red.

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