

ANSWERING REVIEWERS

August 31, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 20836-Revised manuscript.doc).

Title: Multimodality treatment strategies have changed prognosis of peritoneal metastases

Author: Corneliu Lungoci, Aurel Ion Mironiuc, Valentin Muntean, Traian Oniu, Hubert Leebmann, Max Mayr, Pompiliu Piso

Name of Journal: *World Journal of Gastrointestinal Oncology*

ESPS Manuscript NO: 20836

The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated
2. Revision has been made according to the suggestions of the reviewer

Reviewer 1

Comment: The language of the manuscript needs a slight review by a native English translator expert of medical scientific publications.

Response: As suggested by the reviewer the revised manuscript was checked for the English correction with the help of native English language speaking person.

Comment: Particularly: The legend of Figures 1,2,7,10 do not explain well the figures.

Response: The legends of Figures 1, 2, 7, 10 were detailed, for a better understanding of the readers.

Figure 1. Kaplan-Meier survival curve of non-gynecological peritoneal carcinomatosis, stratified according to the Gilly staging system (Stage 0, 1 and 2 vs. Stage 3 and 4)

Figure 2. Kaplan-Meier survival curve of metastatic colorectal cancer stratified according to the metastatic locations (peritoneal carcinomatosis vs. non peritoneal carcinomatosis) and chemotherapy protocols (fluorouracil, leucovorin and oxaliplatin; fluorouracil, leucovorin and irinotecan; irinotecan and oxaliplatin)

Figure 7. Overall survival compared with disease-free survival for pseudomyxoma peritonei (A) and colorectal peritoneal carcinomatosis (B), treated with CRS-HIPEC, from Netherlands

Figure 10. Kaplan-Meier survival curve of colorectal peritoneal carcinomatosis stratified according to hepatic involvement (peritoneal carcinomatosis alone vs. peritoneal carcinomatosis with hepatic metastases)

Comment: The legend of Figure 8 seems wrong (A and B are inverted?).

Response: The error of the Figure 8 A legend was revised, according to the figure content.

Figure 8. Kaplan-Meier survival curve of colorectal peritoneal carcinomatosis treated by CRS-HIPEC, stratified according to the size of residual tumors (A) and the number of regions with residual tumors (B).

Reviewer 2

Comment: The manuscript does not give conclusions about the best indications for Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy based on cancer origin.

Response: Necessary modifications were incorporated in the conclusion, as suggested by the reviewer.

It is important to statement the patients with colo-rectal, appendicular, gastric, and ovarian peritoneal carcinomatosis, as well as patients with pseudomyxoma peritonei and peritoneal malignant mesothelioma must be informed about CRS-HIPEC as a valid

treatment resource. The eligibility criteria for patients' selection will be assessed by multidisciplinary teams, in high level, dedicated treatment centers, according to the performance index, PCI, histological grading, the perspective to obtaining a complete CRS, and the availability of sustaining chemotherapy protocols.

Comment: I suggest the authors rewrite the manuscript by critically analyzing the available evidences from all different cancer histology instead of describing all data together. Some tables summarizing the data reported by the authors should be included to help the reader to follow the authors' proposal.

Response: The manuscript has proposed an approach from the perspective of evolution of multimodal treatment strategies for peritoneal metastases, to offer a fundament for understanding the philosophy of such a treatment. Also, the data reported were stratified, according to the importance/impact of the study type (randomized clinical trials, meta-analysis of randomized clinical trials, multi-institutional studies, systematic reviews, and significant single center experience), not to the primitive tumor entities (as other existent review type researches). Such an approach allows us a comparative analysis of the different tumor entities. In this context, your recommendation to highlight the different tumor entities is extremely welcome and thanks you. We highlight the primitive tumor origin in the manuscript (and the source study type) and revised the results of CRS-HIPEC treatment, assessed by median survival, according both to tumor entities and study type in the Table 1. At the same time, we summarized the key aspects of the evolution of multimodal treatment strategies discussed in this manuscript, for better understanding of the readers, in the Table 2.

Table 1. CRS-HIPEC median survival, related to the tumor entities and study type

Primitive tumor origin	Study type	Median survival (months)
Colorectal	randomized clinical trials	22.3 ^[35]
	single center experience	33 ^[53] , 34.7 ^[45]
	systematic reviews	13-29 ^[54]
	multi-institutional studies	33 ^[52]
Gastric	randomized clinical trials	11.3 ^[46] , 11 ^[47]

Pseudomyxoma peritonei	single center experience	104 ^[53]
	multi-institutional studies	130 ^[52]
Ovarian	multi-institutional studies	35.4-45.7 ^[51]
	systematic reviews	22-54 ^[55]
Malignant peritoneal mesothelioma	systematic reviews	34-92 ^[56]

Table 2. Key aspects and PM model in the evolution of multimodal treatment strategies

period	PM treatment	Key aspects	PM model
All the period	“Conventional” systemic chemotherapy	- significant lower survival for PM vs. other type of metastases	- colo-rectal
1950-1980	“Dedicated” intraperitoneal treatment - Palliative treatment	- the basis for developing further cytostatic drugs	- malignant ascites
1980-2000	“Dedicated” intraperitoneal treatment - Multimodal radical treatment	- regional intraperitoneal normothermic and hyperthermic chemotherapy - peritonectomy procedures - define PCI and CCRS	- appendicular
2000-2010	Multimodal radical treatment - confirmation, aspects, patient selection, controversies	- significant higher survival vs. palliative surgery and diverse systemic chemotherapy regimes - acceptable morbidity and mortality, no significant risk for medical team - respect de learning curve - high costs - define the prognostic factors - position of oncologists - comparison with hepatic	- colo-rectal - appendicular - pseudomyxoma peritonei - malignant peritoneal mesothelioma - gastric - ovarian - PM with hepatic metastases

		metastases	
2010-2014	Multimodal treatment	- PM prophylaxis	- high-risk patients
	research pathways	- laparoscopic HIPEC	for developing PM
		- integration of chemotherapy	- recurrent PM
		with surgery	
		- extension of CRS	

Reviewer 3

Comment: Excellent and exhaustive review

Response: /

Reviewer 4

Comment: Excellent review

Response: /

Scientific editor comments

Step 1. Please revise your manuscript according to the reviewers' comments. To access the reviewers' comments, please log into the Express Submission and Peer-review System (ESPS) by entering your registered e-mail: Pompiliu.Piso@barmherzige-regensburg.de and user password: 159299 under the "Author Track Manuscripts" heading at <http://www.wjgnet.com/esps/trackmanuscript.aspx>. You are expected to address each of the points raised by the reviewers in a response letter that is to accompany your resubmission. Please download the manuscript file edited by the editor, located in the "Manuscript" column, by clicking the link and the title line. You will find the editor's suggestions in the edited manuscript file, which have been added using the Track Changes function. All of the revisions that you make to the revised manuscript should be cited in the response letter and highlighted in the updated version of the manuscript. In order to continually improve the quality of peer-review for our journals, we urge authors to carefully revise their manuscripts according to the peer-reviewers' comments and we promote productive academic interactions between the

peer-reviewers, the authors, and our readers. To this end, we include each of the reviewers' comments, in an anonymized manner, as well as the authors' responses along with the manuscript's publication online.

Response: We carefully revised the manuscript according to the reviewers and editors comments. All the necessary documents are provided along with the revised manuscript.

Step 2. Please update the manuscript according to the Guidelines and Requirements for Manuscript Revision-Review. You can find the Guidelines and Requirements for Manuscript Revision-Review, which includes the detailed writing requirements for the Title, Running Title, Authorship, Abstract, Keywords, Core Tip, Academic Rules and Norms, Tables and Illustrations, Comments and References, as an attachment.

Response: The revised manuscript is updated according to the Guidelines and Requirements for Manuscript Revision-Review.

Step 3. Please provide an Audio Core Tip. In order to attract readers to read your full-text article, we request that the author make an audio file describing the final core tip of the manuscript. This audio file will be published online, along with your article. Acceptable file formats are .mp3, .wav, or .aiff.

Response: The core tip was provided as an audio mp3 file.

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Response: A certificate of Plagiarism report of the manuscript received from the university publication oversight committee and google scholar search of the title are provided as PDF along with the revised manuscript.

Step 5. Please provide the files related to academic rules and norms. The files related to academic rules and norms include the conflict-of-interest statement. You can find the

detailed requirements in the Guidelines and Requirements for Manuscript Revision-Review and in the Format for Manuscript Revision-Review, both of which are provided as attachments.

Response: All the authors declared no conflict of interest. The signed copy of the conflict of interest was provided along with the revised manuscript.

Step 6. Please revise the language of your manuscript. For manuscripts submitted by Non-Native Speakers of English, the authors are required to provide a language editing certificate, which will serve to verify that the language of the manuscript has reached Grade A. You can find the details of the language editing process for manuscripts submitted by Non-Native Speakers of English at http://www.wjgnet.com/bpg/navdetail_85.htm.

Response: The revised manuscript was carefully checked for the English correction with the help of native English language speaking person.

Step 7. Please sign the Copyright Assignment form. The Copyright Assignment form can be downloaded from the ESPS; you may find it under the "Files Download" area (please click on the "+" in front of the manuscript number to view the Files Download button). Please note that the information in the signed document (i.e., the manuscript title, the authors' list, and the corresponding author) must be identical to the information presented in the final version of the manuscript. Please do not fax the signed documents, but instead submit the scanned PDFs online or by e-mail.

Response: The copyright assignment form signed by all the authors is attached as PDF file along with the revised manuscript.

Step 8. Submit the revised manuscript and all related documents. When you are ready to resubmit your revised paper and all required accompanying documents, please click

<http://www.wjgnet.com/esps/ModifyManuscript.aspx?UserId=UUcCdb1Nr3u999mUqbyo79iMzP7wpw2wnL0Lw%2bzOqn1VQ1DzxQjjAMAF2%2f0NT9dF&id=tXWXphUItzW1qN11n61sIg%3d%3d&UserNumId=00026162> to begin the uploading process. Please note that the author list and affiliations, author contributions and funding information are not allowed to be modified after a manuscript's formal acceptance.

Response: We thoroughly checked the names and affiliations of all the authors. We also provided the funding information.

3. References and typesetting were corrected

With the hope the revised manuscript may be considered for publication in the *World Journal of Gastrointestinal Oncology*, thank you for your support.

Sincerely yours,

Pompiliu Piso, Professor of Surgery, Dr. Dr. Honoris Causa
Clinic of Visceral and General Surgery
Krankenhaus Barmherzige Brüder, Academic Teaching Hospitals of the University Regensburg
86 Profeninger street, Regensburg 93049, Bavaria Province, Germany
E-mail: pompiliu.piso@barmherzige-regensburg.de
Telephone: +49941369-2201, Fax: +49941369-2206