

Regensburg, February 27, 2023

Dear Professor Andrzej S Tarnawski, Editor-in-Chief,
Dear Lian-Sheng Ma, Founder and CEO,
Dear Managing Editor,
Dear Reviewers,

On behalf of my fellow authors, first of all, I would like to thank you for your attention and opinion on our original article entitled "Clinical data analysis of primary gastric cancer patients with peritoneal metastases, who underwent cytoreductive surgery with HIPEC". We are grateful that you have found it to be interesting and potentially suitable for publication in World Journal of Gastroenterology.

As requested by the reviewers, the title of the article was changed, and a few necessary modifications were applied to the manuscript. Some minor changes due to spell checking issues had been addressed throughout the manuscript as well.

Here we provide answers to the questions the Company editor-in-chief and our Reviewers raised.

Comments of the Company editor-in-chief

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based

open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>. We thank the well detailed suggestions and instructions of the Company editor-in-chief. The manuscript was revised accordingly.

Reviewer #1:

It is a very good paper.

Thank you for your kind comment our article!

Reviewer #2:

Good work! There are several questions!

Thank you!

1: What are the indications for this type of surgery?

Today, peritoneal metastasis of colorectal carcinoma (including the appendix), rare pseudomyxoma peritonei associated with low-grade mucocoele of the appendix and - with significant limitations - peritoneal metastatic gastric carcinoma are indications for cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). In addition, multimodal therapy is also effective in primary peritoneum malignancies (malignant mesothelioma, primary carcinoma).

Is there a discussion of multidisciplinary treatment?

In Germany, every single case is discussed by a multidisciplinary board of experts from different fields of medicine - oncologists, surgeons, anesthesiologists - before any treatment.

How to determine the scope of surgery?

Preoperatively the surgeons assess the extent of peritoneal dissemination by using abdominal and chest CT scans and diagnostic laparoscopy. The definitive extent of surgery depends on the intraoperative findings and is defined by the goal to reach an CCR0/1 situation, that means no residual disease respectively residual nodules measuring less than 2.5 mm.

2: The probability of postoperative complications is high for this type of surgery, so how is it controlled?

All patients have to attend to an anesthesiologists prior surgery, where it is decided whether any preoperative prehabilitation is necessary, such as optimization of nutrition intake with the help of nutritionists, recognition and treatment of iron

deficiency anemia, etc. This is part of the “Enhanced recovery after surgery” (ERAS)-protocol, which is routinely used in our institution.

After the CRS + HIPEC procedure, close surveillance and treatment at an intensive-care unit is needed. In a reverse-isolation for 48 hours, all patients receive special care, routine checks of different postoperative blood parameters, and the beginning of mobilization of the patient also starts. When patients are in a stable cardiopulmonary status, they can leave the ICU.

But all in all, one goal of this study was to proof our experience, that the probability of postoperative complications is not significantly higher and CRS + HIPEC is a safe procedure.

3 : Is preoperative PET-CT routinely performed?

PET-CT scans are not mandatory to perform this type of surgery. As detailed above, abdominal and chest CT scans and diagnostic laparoscopy are needed prior CRS + HIPEC. It has to be mentioned however, that if the patient’s oncologist considers it necessary to perform a PET-CT prior the surgery, it will be performed.

Reviewer #3:

This is a very well organized manuscript with very objective evaluations about the shortcomings of the study such as heterogenous patient groups and low number of patients. However, even though not being substantial, it is promising to see HIPEC makes a difference to some extent for the patients with peritoneal carcinomatosis in the treatment of this difficult disease. The manuscript is worth publishing as it may guide possible future prospective studies.

Thank you for the kind comment on our manuscript.

Reviewer #4:

The authors have looked at a difficult topic, advanced gastric cancer patients with peritoneal metastasis where CRS and HIPEC was performed. They conducted a retrospective analysis of 73 patients with CRS followed by HIPEC, they confirmed applied over 90-minutes has a positive impact on disease-specific survival in comparison with CRS followed by 60-minutes of HIPEC and presented patients treated with neoadjuvant trastuzumab had significantly better DSS. Unfortunately, there are similar recent studies in the literature, *Eur J Surg Oncol.* 2019 Sep;45(9):1734-1739.

Thank you for your kind criticism. Roth et al. showed that there is a postoperative secondary peak of inflammation in patients without clinical postoperative complications, which have been also associated with longer duration of HIPEC and with non-oxaliplatin based chemotherapeutics. This is an interesting result, which underlines that there is a reaction of the immune system on HIPEC and it’s depending on the duration of circulating chemotherapeutics. Further discussion on this topic was added to our manuscript.

The current study had a few limitations, including the small sample size, the single-center retrospective nature of the study, and the heterogeneity of the data. During the time of evaluation, the protocols concerning the preoperative chemotherapy treatment did significantly change. Furthermore, in this small cohort of patients with GC and PM there was only very limited data on post-HIPEC treatment.

Thank you for the criticism, we agree with it. Efforts were made to collect any post-HIPEC data of the patients, however, we could not collect these in a timely manner, as patients' routine oncological treatments were performed in another hospitals. Limitations of our study was revised accordingly.

Reviewer #5:

Clinical data analysis of primary gastric cancer patients with peritoneal metastases, who underwent cytoreductive surgery with HIPEC *General: The manuscript contains a retrospective study of 73 patients with peritoneal metastasis of gastric origin who underwent cytoreductive surgery and HIPEC.

*Title: The title could be improved as it does not give any clue about the findings of the study. I would recommend something like: "Prolonged HIPEC duration with 90 minutes cisplatin might increase overall survival in gastric cancer patients with peritoneal metastases"

Thank you for your comment and suggestion. We have changed the title accordingly.

*Abstract: Abstract is correct. Conclusion may not be adequate. As the study does not compare HIPEC with no HIPEC we could not conclude that.

Thank you for your kind criticism. Conclusion of the abstract was changed accordingly.

*Background: Introduction is quite long. first paragraph should be shortened to less than a half.

Thank you, it has been shortened.

*Material & Methods: The authors should explain better its protocol, especially regarding perioperative chemotherapy as later it is an important part of the study. It should stay clearly as well if they perform diagnostic laparoscopy in all patients and which is the management of positive cytology. How was laparoscopy preformed, was the current Sugarbaker's recommendations followed? Sugarbaker PH et al. Laparoscopy technique in the setting of peritoneal metastases to avoid port site relapse. Surg Oncol 2021; 37: 101543.

Chemotherapy was administered in accordance with the German guideline on gastric cancer. Chemotherapy drug recommendation changed from EOC to FLOT after Al-Batran's FLOT-4 study in 2019. In addition, diagnostic laparoscopy is also performed from T3 stage and/or CT morphological evidence of peritoneal carcinomatosis. This was changed according to Sugarbaker. (Sugarbaker PH et al. Laparoscopy technique

in the setting of peritoneal metastases to avoid port site relapse (Surg Oncol 2021; 37: 101543). All additional information has been incorporated into patients and methods.

[There is no mention of thiosulfate, is it used to protect the kidney?](#)

Thank you for the important hint. During the observation period of the study we did not administer sodium thiosulfate during the HIPEC procedure to protect the kidneys, as at the time there were only a few and very limited data available. However, since January 2022 we routinely use sodium thiosulphate as more information on this topic came to light and showed the additional benefit of administering it (DOI: 10.1080/02656736.2020.1795277 and 10.1245/s10434-021-10508-x).

[It should be stated that 90-days complications by Clavien-Dindo Classification or NCI-CTCAE classification were recorded, mortality should be in 90 days too.](#)

Definition of post-HIPEC / post-procedure death was updated in Methods as follows. *“Although some recent publications suggest including all patient deaths within 90 days as post-procedure death, HIPEC related post-procedure deaths were defined as follows: 1.) It had to occur during our observation period at the intensive-care unit or at the surgical inpatient unit prior the discharge of the patients, or 2.) between discharge and adjuvant chemotherapy. If a patient started adjuvant chemotherapy, their death was defined as GC-related.”*

[*Results: A flow chart will help to understand the inclusion and main outcomes of the study.](#)

Thank you for the suggestion. A figure about the study had been included.

[The authors refer that “The need to remove any further organs than the ones detailed in Supplementary Table 1 during CRS \(N = 9\) was associated with a negative effect”. Please explain which organs were resected that are not specified in the table. Sup Table 1 should be included in the main paper as it describes the population of study.](#)

The text was updated to include all the necessary information as follows. *“The need to remove any further organs, such as the removal of the bladder or the appendix during CRS”*.

Thank you for the suggestion to move Supplementary Table 1 into the main text, however, we believe a 4-page table is too long to be included in the main file. Moreover, most of the presented data is not different between the two study cohorts.

[There is a reduced number of patients who received trastuzumab \(n=5\) with such a sparse number is hazardous to establish a clear benefit.](#)

All sentences regarding trastuzumab were revised and refined.

[The authors “marginally better RFS was found in those patients who did not have to undergo peritonectomy of the pelvis \(HR: 0.3382; 95% CI: 0.1099 – 1.0410; P = 0.0588\)”. Nevertheless, CI includes 1, so it should not be interpreted like that.](#)

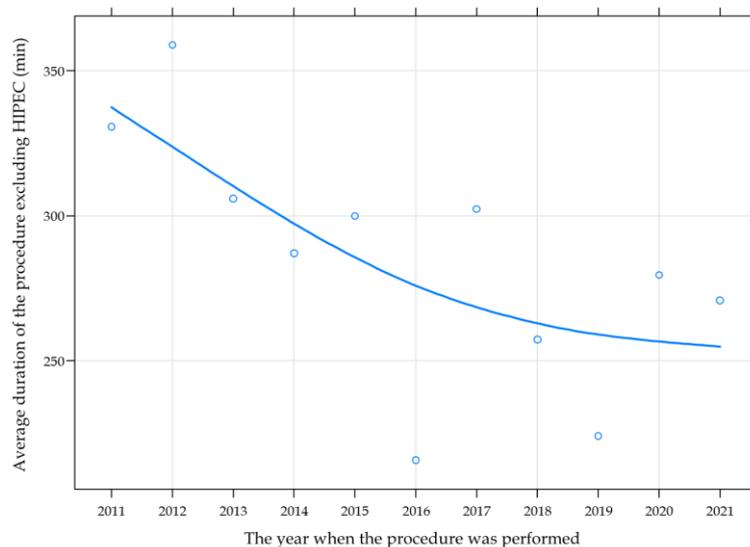
Thank you for the kind criticism. The sentence was revised as follows: *“Furthermore, tententiously longer RFS was found in those patients...”*

*Discussion: The authors state that “An important conclusion of the presented studies and our novel results is that patients with small tumor burden (PCI < 6, but maximally 9) benefit the most from this multimodal therapy”. Nevertheless, the data given shows “DSS of patients were marginally affected by the duration of HIPEC [60 (ref.) vs. 90 min: HR: 0.5252; 95% CI: 0.2565 – 1.0750; P = 0.0781] and by PCI (HR: 1.0630; 95% CI: 0.9982 – 1.1310; P = 0.0569), and significantly by preoperative serum CEA levels (HR: 1.2220; 95% CI: 1.0880 – 1.3720; P = 0.0007).” So that affirmation is not supported by the data of this paper.

The sentences were updated as follows: “An important conclusion of the above presented studies is that patients with small tumor burden (PCI < 6, but maximally 9) benefit the most from this multimodal therapy. Although in the current study we could not justify the statistically significant benefit of reduced PCI scores, our results were in line with the previously described observations: patients with higher PCI scores had tendentially shorter survival.”

It is stated that “Furthermore, an interesting observation emerged during the analysis of our data that in the course of time and an increasing number of cases, the duration of surgery to reach complete cytoreduction has become shorter.”. Please provide data effectively showing this progression towards lesser times in the theatre as it is an interesting learning curve point. It is stated right after talking about the learning curve that “In the current analysis, the median survival time was 27.30 mo in the 90-minute group, which was significantly longer than that of the 60-minutes group (12.86 mo).” It should be indicated that the learning curve could have affected this outcome.

Thank you for your suggestion. The data on operating times was further analyzed and it was found that there was a statistically significant continuous improvement over time in our surgical center ($p = 0.0097$). A figure was also introduced to represent this observation:



Moreover, the following was revised and added to Discussion: “Furthermore, an interesting observation emerged during the analysis of our data that in the course of time and an increasing number of cases, the duration of surgery to reach complete cytoreduction has become significantly shorter. These findings match with the results of a study outlining the

technical aspects and learning curve of CRS/HIPEC of Vining et al., where the authors describe a steep learning curve and a relation of the completeness of cytoreduction and the surgeons' expertise (DOI: 10.1002/jso.25939)."

It is stated that "Moreover, we could make the observation that if the procedure of ovariectomy or peritonectomy of the pelvis during CRS is not necessary, the RFS of the patient improved". As mentioned before, this is not supported by the data. As mentioned before, I would recommend including learning curve and experience of the team as a potential bias in limitations.

Thank you for bringing this issue to our attention. Our data showed that peritonectomy of the pelvis is associated with shorter OS and not with RFS. The sentence was updated accordingly as follows: *"Moreover, we could make the observation that if the procedure of peritonectomy of the pelvis during CRS is not necessary, the OS of the patient improved. We hypothesize that the extent of the tumor manifestation may have a bigger influence on patient survival than its histopathological differentiation. We assume that the improvement in patient survival may also be based rather on the advanced extent of the malignant disease than on the biology of the tumor, moreover, the learning curve in the experience of the surgical team might have also introduced some additional bias."*

Discussion is quite long and has some parts that are too speculative. I would recommend the authors to focus on the main findings of the paper and reduce the review of the current state of the art in literature.

Discussion was thoroughly revised focusing only on the main findings.

Conclusions should be based on results of the study. So, I would recommend stripping the final paragraph of all recommendations that are not strictly produced by the study results (prehab, anemia, modern treatments...). Moreover, I would be more cautious pointing out benefit of 90 over 60 due to potential bias.

Thank you for your kind criticism and suggestion. The Conclusion was revised accordingly.

Yours sincerely,

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