



Budapest, April 26, 2021

Dear Professor Monjur Ahmed, Professor Florin Burada, Professor Rosa M Jimenez Rodriguez, and Professor Pashtoon Murtaza Kasi,

Dear Reviewer,

Dear Science Editor,

On behalf of my fellow authors, first of all, I would like to thank you for your attention and opinion on our review article entitled “Evidence based tools to improve efficiency of currently administered oncotherapies for tumors of the hepatopancreatobiliary system”. We are grateful that you have found it to be interesting and suitable for the publication in World Journal of Gastrointestinal Oncology.

Our answers to the comments raised in the reviews are given below.

### **Reviewer**

*The authors have summarized information about using adjuvant hyperthermia in hepatopancreatobiliary cancers. The manuscript is well written with clear language communication. The figures and table are appropriately presented.*

Thank you for your positive comments on our manuscript and for your recommendation to publish the paper.

*The reviewer's question is whether the staging, for each type of cancer such as tumor sizes and metastatic status, of the cancers mentioned would be associated with the outcomes of the treatment. Is this already included in the summarized information in the figures and table.*

In most cases, hyperthermia is used in patients with advanced or metastatic malignancies with no probability of cure with conventional treatments (Stage III, but in the majority Stage IV). In a few studies, which have been marked with a “+” in the revised Table 1, Stage I and II patients were also included, however, no analysis was performed on how much staging exactly affects hyperthermia (e.g. a Cox model to get HRs). Furthermore, to our knowledge, no study investigated hyperthermia in lesser stage cancers due to the known high efficacy of conventional treatment

options. In the CERT study (ref.nr. 44) the effect of tumor size (<5 cm vs. ≥5 cm) on local progression-free, progression-free and overall survival has been analyzed: in univariate models the larger-sized tumor were described as poor prognostic signs, but the same could not be justified in multi-variate Cox models.

In addition to the extension of Table 1, the following paragraph was added to Conclusion: *“The application of hyperthermia has not found its exact clinical indication in the setting of stage. For most patients, this is a palliative treatment, when no other possibility is available in the traditional oncological armamentarium. Thus, a refined or subdivided stage 4 category would be most beneficial to stratify these patients according to tumor load, involved organs or supplemented by serum tumor marker level. Tumor marker like lactic dehydrogenase as used e.g. in melanoma stage 4 subdivision might be an option<sup>[76]</sup>. Certain organs, which are vital or less crucial could also be taken into account when containing metastases. To our knowledge, no such classification exists for the hyperthermia treated patients' stratification. Eastern Cooperative Oncology Group performance status, body fluids (ascites, hydrothorax, other edema) may be limitations in the administration of hyperthermia. In future analyses, it is encouraged to address the question of tumor load and the capabilities of the patient to overcome the neoplastic disease.”*

### **Science Editor**

*A total of 75 references are cited. There is 1 self-cited reference. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations (i.e. those that are most closely related to the topic of the manuscript) and remove all other improper self-citations.*

Modulated electro-hyperthermia (mEHT) is one of the newest advancements in hyperthermia, and only a small number of clinical studies and even less reviews are available. To our knowledge, only two reviews are available about mEHT and various cancers, one focusing on cellular- and animal model systems (Krenacs et al., PMID: 32872532), and one focusing on the clinical applications (Szasz et al., ref.nr. 24 in our manuscript). Due to the clinical focus of our manuscript, we decided to include the aforementioned review article of Szasz et al., instead of including a wider range of articles about not-closely-related model-studies and/or deeply-technical descriptions about mEHT.

*The “Author Contributions” section is missing. Please provide the author contributions.*

Author Contributions have been included. Furthermore, the manuscript has been revised as per the instructions given in *“Guidelines and Requirements for Manuscript Revision: Minireviews”*.

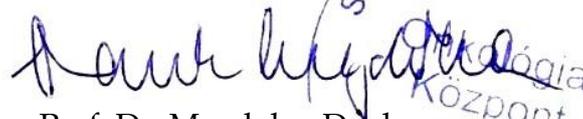
*The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s).*

A certified notification about the winning of the grant has been attached to the submission.

*The authors did not provide original pictures. Please provide the original figure documents.*

As per instruction of the BPG guidelines, all figures have been uploaded as a single PowerPoint file.

Yours sincerely,

  
Prof. Dr. Magdolna Dank  
Semmelweis University

