

Dear Dr. Fiorentini,

We are pleased to inform you that, after preview by the Editorial Office and peer review, as well as CrossCheck and Google plagiarism detection, we believe that the academic quality, language quality, and ethics of your manuscript (Manuscript NO.: 64774, Observational Study) basically meet the publishing requirements of the World Journal of Clinical Oncology. As such, we have made the preliminary decision that it is acceptable for publication after your appropriate revision. Upon our receipt of your revised manuscript, we will send it for re-review. We will then make a final decision on whether to accept the manuscript or not, based on the reviewers' comments, the quality of the revised manuscript, and the relevant documents. Please follow the steps outlined below to revise your manuscript to meet the requirements for final acceptance and publication.

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Please resolve all issues in the manuscript based on the peer review report and make a point-by-point response to the issues raised in the peer review report. Authors must resolve all issues in the manuscript that are raised in the peer-review report(s) and make point-by-point responses to the issues raised in the peer-review report(s), which are listed below:

Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade A (Priority publishing)

Conclusion: Major revision

Specific Comments to Authors:

1. In ABSTRACT (page5), what's the difference between "locally advanced pancreatic cancer (line10) "and" stage III-IV pancreatic cancer (line13) "? Please clarify the tumor staging method.

Author response: we amended the definition of pancreatic cancer: stage III and IV pancreatic cancer, because we included also metastatic patients.

2. Page11, According to the drug instructions, gemcitabine has a half-life of 42-94 minutes, and gemcitabine is completely eliminated within 5-11 hours after infusion. How to combine high drug blood concentration with the modulated electro hyperthermia and optimize their synergy if mEHT was administered after CHT or within 48 hours?

Author response: The vast majority of treatments containing gemcitabine was administered on the same day as electro-hyperthermia treatment. In a minority of patients for reasons of precarious clinical

conditions and geographic accessibility it was administered the following day or within the following 72 hours. Even if the drug instructions elaborated by the manufacturer show that gemcitabine has a half-life of 42-94 minutes, and gemcitabine is eliminated within 5-11 hours after infusion, the pharmacokinetic elimination half-life for dFdU varies between 2 and 24 h, and it is still present systemically in concentrations greater than 1  $\mu$ M up to 1 week after dosing (Peters GJ, Clavel M, Noordhuis P, Geysen GJ, Laan AC, Guastalla J, Edzes HT, Vermorken JB. Clinical phase I and pharmacology study of gemcitabine (2', 2'-difluorodeoxycytidine) administered in a two-weekly schedule. J Chemother. 2007 Apr; 19 (2): 212-21. Doi: 10.1179 / joc.2007.19.2.212. PMID: 17434832.)

3. Page 12 line 1-2, What is the version of RECIST? Is it version 1.4? Author response: We used RECIST 1.4

4.3. Page 13, Some differences were found between CHT+ mEHT and CHT groups in median age (64 vs 69 years,  $p=0.013$ ), previous RT (2% vs 12%,  $P=0.023$ ), number of previous CHT lines (2 lines: 19% vs 35%,  $p=0.037$ ) and type of chemotherapy. Gemox was the most used chemotherapy in CHT+ mEHT group ( $p=0.004$ ), whereas FOLFOX and FOLFIRINOX were used only in CHT group ( $p<0.05$ ). Are the two groups comparable? In particular, the two groups of chemotherapy efficacy is different.

Author response: The differences between CHT+mEHT and CHT groups in median age, previous RT, number of previous CHT lines and type of chemotherapy they are due to the time in which the study and the recruitment of patients were developed. These statistical differences are minor and acceptable in a case control study like ours. FOLFOX and FOLFIRINOX are newer therapeutic regimens than GEMOX and have been preferred by clinicians who have treated patients in the first instance. This study would not have been possible if we had chosen to use only one type of chemotherapy.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This observational study aims to compare mainly disease-free outcomes of chemotherapy versus its association with electro-hyperthermia for the treatment of locally advanced pancreatic cancer (stage III-IV): Despite of the potential bias inherent to the retrospective nature of the study and as consequence a general heterogeneity of the population in analysis... its is a very well-designed study, with proper statistical methods and minor english discordances.... the review about the subject was widely performed...and the conclusions of the study was properly in accordance with the proposed methods and analysis.

Author response: thank you very much for your comment, We reviewed the language

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This observational pilot study provides effective evidence that mEHT association to chemotherapy can enhance its benefit in pancreatic cancer patients. Despite that these results are not verified in a large cohort study, we found it some decision-making roles to the treatment of pancreatic cancer. Combination of mEHT and chemotherapy might be effective therapy. However, there are still some questions.

1. PR, CR, PD should be clarified in methodology. Author response: we clarified the PR, CR, PD

2. Age should not be considered an issue, since the improvement of survival and tumor response was observed also in older patients (>65 years) with locally advanced pancreatic cancer. Why did the authors not conduct subgroup analysis? Does age interfere with research results?

Author response: We did not perform a subgroup analysis because the number of patients treated was not sufficient to have reliable data. Furthermore, the onset of pancreatic cancer is consistently higher in the 60s and 70s. This makes the sample homogeneous and allows a correct statistical evaluation as we have performed.

3. In Overall survival (OS) analysis, the survival curve is crossed, please explain the reason and make further analysis.

Author response: In Overall survival (OS) analysis, the survival curve is crossed, for the reason that stage III-IV pancreatic cancer is always a fatal disease and inevitably comparing the curves of 2 treatments these crossed because all patients will die. To verify the positive results of a study it is better to evaluate the percentage of survivors at 3, 6, 12 months and also the evaluation of the duration of the responses are the most important data to define the validity of the results.

4. The authors demonstrated some imbalances distribution between the two subgroups as concerning number of patients and median age. What effect and influence will have on the stability of the results?

Author response: The some imbalances distribution, observed by Reviewer 3, between the two subgroups as concerning number of patients and median age do not influence the final result because the range of age is substantially reduced to decades 60 and 70.

#### 4 LANGUAGE QUALITY

Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

#### 5 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor: 1 Scientific quality: The manuscript describes an observational study of the modulated Electro-Hyperthermia as palliative treatment in stage III and IV pancreatic cancer. The topic is within the scope of the WJCO.

(1) Classification: Two Grades B and Grade D;

(2) Summary of the Peer-Review Report: It is a very well-designed study, with proper statistical methods and minor English discordances. The questions raised by the reviewers should be answered;

(3) Format: There are 2 tables and 2 figures;

(4) References: A total of 22 references are cited, including 13 references published in the last 3 years;

(5) Self-cited references: There are 5 self-cited references. 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. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; **Author response: we removed improper self citations**

(6) References recommendations: The authors have the right to refuse to cite improper references recommended by the peer reviewer(s), especially references published by the peer reviewer(s) him/herself (themselves). If the authors find the peer reviewer(s) request for the authors to cite improper references published by him/herself (themselves), please send the peer reviewer's ID number to [editorialoffice@wjgnet.com](mailto:editorialoffice@wjgnet.com). The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately.

2 Language evaluation: Classification: Two Grades A and Grade B.

3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the Institutional Review Board Approval Form, and the written informed consent. No academic misconduct was found in the Bing search.

4 Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJCO.

5 Issues raised: (1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; **Author response: we provided the pictures in ppt file**

(2) PMID numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout. **Author response: we added PMID number to the references when available**

6 Recommendation: Conditional acceptance.

(2) Editorial office director:

(3) 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 Clinical Oncology, 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. **The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words).**

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Best regards,

Lian-Sheng Ma, Science Editor, Company Editor-in-Chief, Editorial Office

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