

To:

Lian-Sheng Ma

Editor-in-Chief

June 28th, 2021

World Journal of Gastrointestinal Oncology.

Re: Revised version Manuscript NO: 66203

Dear Editor,

We would like to thank you and the reviewer for your interesting comments and constructive criticisms of our invited manuscript entitled: " Current status of non-surgical treatment of locally advanced pancreatic cancer" that was submitted for publication in the World Journal of Gastrointestinal Oncology.

We have followed the reviewer's and Editor's remarks and hope that we address all comments adequately. We have submitted a point-by-point list of all the changes made and a clean revised manuscript. The authors also provided the original ppt file with the two figures. Please note that these figures originate from the authors personal work and do not require permissions.

Yours sincerely,

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Point by point reply

Reviewer #1:

Specific Comments to Authors: Dear Authors, thank you for sharing your article. Non-surgical treatment of locally advanced pancreatic cancer is a very interesting and complex topic, considering that approximately 30%-35% of pancreatic cancer patients present with locally advanced disease at diagnosis, but only a small proportion of them manage to go to surgery after neoadjuvant treatment.

Manuscript is well written, I suggest the following modifications: - You should consider to discuss if there are studies that investigated (or are investigating) SBRT vs “conventional” radiotherapy - In the paragraph “ABLATIVE TECHNIQUE” I suggest discussing also the role of reversible electrochemotherapy for a matter of consistency. For example: Casadei R, Ricci C, Ingaldi C, Alberici L, Di Marco M, Guido A, Minni F, Serra C. Intraoperative electrochemotherapy in locally advanced pancreatic cancer: indications, techniques and results-a single-center experience. *Updates Surg.* 2020 Dec;72(4):1089-1096. doi: 10.1007/s13304-020-00782-x. Epub 2020 May 12. PMID: 32399592.

Authors' reply: The abovementioned issues were addressed in two newly introduced paragraphs. One in the “RADIOTHERAPY” section as follows: “Only few, non-randomized, retrospective studies compared SBRT and conventional fractionated RT [66, 67] in the local advanced pancreatic cancer curative or neo-adjuvant setting. SBRT was associated with significantly improved overall survival compared to conventional fractionated RT and, additionally, SBRT was associated with significantly increased rates of pathological complete response and margin-negative resection in neo-adjuvant setting. These are promising results and provide the basis for consideration for prospective validation. However, the indication for SBRT in local advanced pancreatic cancer patients may be affected by the high metastatic potential of the disease, causing the loss of its meaning to intensify local treatment.”

Another in the “ABLATIVE TECHNIQUE” section as follows: “Reversible electrochemotherapy (ECT) is a new non-thermal ablation technique that avoids possible thermal injury to the peripancreatic vessels like portal mesenteric vein combining the use of chemotherapeutic drugs (bleomycin) with electric pulses for cell membrane electroporation. A transient cell membrane improve permeability is determined by electric pulses, permitting the exposure of the cell to chemotherapeutic drugs. [19] The procedure is divided into four steps: laparotomy or laparoscopic or percutaneous approach and intraoperative ultrasound to confirm that the pancreatic tumor was unresectable and to exclude distant metastases, needle insertion, bleomycin infusion and electroporation. Eight minutes after the bleomycin infusion, electric pulses were applied and delivered using four single long

needle electrodes having 1.2 mm in diameter, and 3 or 4 cm active part. ECT was performed mostly in young patients (mean age, 63 years), with a good performance status and normal BMI. ECT was safe, according to the absence of acute intraoperative adverse effects related to electroporation and effects related to the bleomycin. [19] Nevertheless there is few studies regarding ECT in literatures [20, 21] and additional studies should be carried out."

Reviewer #2:

Specific Comments to Authors: This is an overall good review on non-surgical therapies for pancreas cancers. The topic is interesting. Following points should be improved. There are many environmental, dietary and lifestyle factors that influence the microbiome (in intestinal lumen, tissue and other body sites), immune system, carcinogenic mechanisms, and response to therapy. The authors should discuss these points; influence of those factors, eg, smoking, alcohol, diet, obesity, microbiome, etc. on tumor and the immune system. These factors may influence response to therapy in each patient differentially. There are also influences of GxE (gene-by-environment interactions). More discussion on interaction of those genetic changes and the environmental factors (mentioned as above) in relation to response to treatment is important. In these contexts, research on dietary / lifestyle factors, microbiome, immunity, and molecular tissue biomarkers is needed for the future direction. The authors should discuss molecular pathological epidemiology which can investigate those factors in relation to molecular pathologies, clinical outcomes, and response to treatment. Such research can be a promising direction and improve prediction of response to therapy. Strengths and challenges of molecular pathological epidemiology discussed in Gut 2011, Annu Rev Pathol 2019, etc. should be discussed in this review.

Authors' reply: The authors would like to thank the reviewer for this comment. Indeed, genetic, and environmental factors both influence the pathogenesis of pancreatic cancer and possibly treatment outcomes. However, as an in detail discussion of the abovementioned data is beyond the scope of this review, the

authors have modified the conclusive paragraph to briefly discuss these significant issues as follows: “As the pathogenesis of LAPD is multifactorial and has been associated with genetic factors (mainly germ-line BRCA2 gene mutations, but also various syndromes such as the Lynch syndrome, hereditary breast and ovarian cancer syndrome, familial adenomatous polyposis and Li-Fraumeni syndrome) environmental factors (obesity, smoking habit, diabetes, alcohol consumption, dietary factors such as red meat consumption, and occupational exposure to nickel cadmium and arsenic, and the human microbiome), future treatment directions should focus on the investigation of these factors to provide personalized therapeutic schemes and improve survival. [2, 63, 64]”