Reviewer 1

1) The title says the results of the treatment results of hyperthermia and chemotherapy in patients with locally advanced pancreatic cancer. Looking at the purpose of the purpose of study, 1. Target patients: locally advanced pancreatic cancer or metastatic pancreatic mass 2. Treatment method: Anticancer treatment alone or in combination with anticancer treatment and heat treatment Therefore, the research title is different from the research purpose

Author response: we amended the title according to study purpose

2) Even in the case of locally advanced pancreatic cancer, the treatment response may vary depending on the clinical stage. However, in the evaluation of treatment response results between the two groups, each stage was not considered. If more advanced stages are included in the chemotherapy alone group, this may be considered as bias in the interpretation of the results.

Author response: the TNM stage in the two groups is not reported in the database, in the inclusion criteria we put stage III and IV in order to facilitate data entry by clinicians essentially wanting to distinguish locally advanced disease from metastatic disease. We judged this suitable for our research

Reviewer 2

It is evident that the authors of this manuscript have put good effort into assess survival, tumor response and toxicity of mEHT for locally advanced or metastatic pancreatic tumor therapy. However, there are several suggestions.

1.I suggest the authors add 1-2 sentences to the abstract, briefly stating the importance, value or innovation of mEHT.

Author response: we added two sentences in the background section of the abstract. "a significant number of researchers reported the useful therapeutic results of regional hyperthermia in association with anticancer chemotherapy (CHT) and radiotherapy for the treatment of pancreatic cancer. A new hyperthermia technique defined as modulated electro-hyperthermia (mEHT) induced immunogenic death or apoptosis of pancreatic cancer cells in laboratory experiments and increased tumour response rate and survival in patients, offering beneficial therapeutic effects against this severe cancer."
"mEHT treatments were performed applying a power of 60–150 watts for 40-90 minutes, simultaneously or within 72 hours of administration of chemotherapy."

2.In the part of introduction, the authors mentioned the relationships between Lynch syndrome, hereditary pancreatitis, Peutz-Jeghers syndrome, cystic fibrosis, BRCA and pancreatic cancer. However, the source of the datas was not mentioned, so I suggest the authors cite several relevant articles to enhance the persuasiveness of this manuscript.

Author response: we added the following references:

- Zalevskaja K, Mecklin JP, Seppälä TT. Clinical characteristics of pancreatic and biliary tract cancers in Lynch syndrome: A retrospective analysis from the Finnish

National Lynch Syndrome Research Registry. Front Oncol. 2023 Feb 1;13:1123901. doi: 10.3389/fonc.2023.1123901. PMID: 36816932; PMCID: PMC9929148.
- Panchoo AV, VanNess GH, Rivera-Rivera E, Laborda TJ. Hereditary pancreatitis: An updated review in pediatrics. World J Clin Pediatr. 2022 Jan 9;11(1):27-37. doi: 10.5409/wjcp.v11.i1.27. PMID: 35096544; PMCID: PMC8771313.
- Tacheci I, Kopacova M, Bures J. Peutz-Jeghers syndrome. Curr Opin Gastroenterol. 2021 May 1;37(3):245-254. doi: 10.1097/MOG.0000000000000718. PMID: 33591027.
- Archangelidi O, Cullinan P, Simmonds NJ, Mentzakis E, Peckham D, Bilton D, Carr SB. Incidence and risk factors of cancer in individuals with cystic fibrosis in the UK; a case-control study. J Cyst Fibros. 2022 Mar;21(2):302-308. doi: 10.1016/j.jcf.2021.07.004. Epub 2021 Aug 1. PMID: 34348871.
- Kindler HL, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, Park JO, Hochhauser D, Arnold D, Oh DY, Reinacher-Schick A, Tortora G, Algül H, O'Reilly EM, Bordia S, McGuinness D, Cui K, Locker GY, Golan T. Overall Survival Results from the POLO Trial: A Phase III Study of Active Maintenance Olaparib Versus Placebo for Germline BRCA-Mutated Metastatic Pancreatic Cancer. J Clin Oncol. 2022 Dec 1;40(34):3929-3939. doi: 10.1200/JCO.21.01604. Epub 2022 Jul 14. PMID: 35834777.

3.The authors mentioned in the the part of results that “The two groups had similar characteristics (table 1).” but did not give the P values, please recheck the table and mark P values.

Author response: we added the p values to table1

4.The authors wrote in the part of results that “Hyperthermia did not affect the chemotherapy toxicity. No increased blood pressure or any other cardiac changes were observed for mEHT sessions in patients who received adequate cardiological monitoring including clinical examination, electrocardiogram and echocardiogram.”, the author discuss the toxicity based on cardiovascular system, how about other systems, such as respiratory system? Only discuss the toxicity about cardiovascular system may be inadequate?

Author response: we assessed the cardiovascular function with with electrocardiogram and echocardiogram, as we specified in the methods section, as concerning the other adverse events were all monitored according to clinical practice and classified using the Common Terminology Criteria for Adverse Events version 5.0; in the results section we also specified that our results shed that Hyperthermia did not increase haematological, hepatic, pulmonary and metabolic toxicity due to chemotherapy.

5.Just as the authors mentioned in this manuscript, similar studies have been done to validate the advantages of mEHT in pancreatic cancer treatment, so what is the innovation of this manuscript, I suggest the authors claim it clearly.

Author response: we underlined the innovation of this study in the discussion section, as follows: “The novelty of this study is the accurate reporting of a significant number of patients treated with mEHT compared with an equally large number of patients who

received second and third-line chemotherapy. Such a large total number of patients, 217, has never been published in the literature."

6.There are many repeated sentences in this manuscript, the authors could use different expressions when express the same result for the second or third time.

Author response: we corrected the text

7.It will be worthwhile to include the following articles during the revision process:

Lechner K., Berger F., Dieterle N., Abdel-Rahman S., Salat C., and Issels R., GEMCITABINE AND CISPLATIN COMBINED WITH REGIONAL HYPERTHERMIA AS SECOND-LINE TREATMENT IN PATIENTS WITH GEMCITABINE-REFRACTORY ADVANCED PANCREATIC CANCER. Annals of Oncology, 2012. 23: p. 62-62.

Liu X., Song J., Zhang H., Liu X., Zuo F., Zhao Y., Zhao Y., Yin X., Guo X., Wu X., Zhang H., Xu J., Hu J., Jing J., Ma X., and Shi H., Immune checkpoint HLA-E:CD94-NKG2A mediates evasion of circulating tumor cells from NK cell surveillance. Cancer cell, 2023. 41(2): p. 272-287.e9.

Gorbaslieva I., Peeters M., Ysebaert D., Saldien V., Rudenko O., Brancato L., van den Bossche J., and Bogers J., A monocentric, first-in-human (FIH), safety and preliminary efficacy study of (neo) adjuvant, model-based, whole-body hyperthermia (WBHT) treatment in advanced solid cancer patients or stage IV metastatic pancreatic adenocarcinoma patients. Journal of Clinical Oncology, 2022. 40(4).

- Author response: we added the above references. As concerning the first reference suggested we added this: Tschoep-Lechner KE, Milani V, Berger F, et al. Gemcitabine and cisplatin combined with regional hyperthermia as second-line treatment in patients with gemcitabine-refractory advanced pancreatic cancer. Int J Hyperthermia. 2013;29(1):8-16. [doi:10.3109/02656736.2012.740764]. that is the definitive study.

8.There are some spelling and grammatical errors in the manuscript. The authors should carefully polish the language.

Author response: we corrected the text