Author’s response to reviews

Title: Irreversible electroporation versus radiotherapy after induction chemotherapy on survival in patients with locally advanced pancreatic cancer: a propensity score analysis

Authors:
Chaobin He (hechb@sysucc.org.cn)
Jun Wang (wangjun@sysucc.org.cn)
Shuxin Sun (sunshx@sysucc.org.cn)
Yu Zhang (zhangyu@gzzoc.com)
Xiaojun Lin (linxj@sysucc.org.cn)
Xiangming Lao (laoxm@sysucc.org.cn)
Bokang Cui (cuibk@sysucc.org.cn)
Shengping Li (lishp@sysucc.org.cn)

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Author’s response to reviews:
Dear Linda Gummlich and reviewers:

I am pleased to submit my revised manuscript entitled “Irreversible electroporation versus radiotherapy after induction chemotherapy on survival in patients with locally advanced pancreatic cancer: a propensity score analysis” (BCAN-D-19-00081). I feel that the reviewers offered helpful and constructive suggestions, and I appreciate the editor and reviewers’ comments. Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. All authors have read and approved the revised manuscript. There are no financial or other relationships that might lead to a conflict of interest. I hope that the revised manuscript will be accepted for publication.

The manuscript has been edited for proper English language, grammar, punctuation, spelling, and overall style by highly qualified native English speaking editors. The manuscript should be English-ready for publication.
Below, I have restated each esteemed reviewer’s comments and have included my response points by points and the changes have been made accordingly in the revised manuscript.

I look forward to hearing from you soon.

With best wishes,

Yours sincerely,

Dr Shengping Li
Department of Hepatobiliary and Pancreatic Surgery
State Key Laboratory of Oncology in South China
Collaborative Innovation Center for Cancer Medicine
Sun Yat-sen University Cancer Center
651 Dongfeng Road East
Guangzhou, Guangdong 510060, P.R. China
E-mail: lishp@sysucc.org.cn
We would like to express our sincere thanks to the reviewers for the constructive and positive comments.

Point-by-point response to commons of the editor and the reviewers

Reviewer 1 evaluation

Pancreatic adenocarcinoma is associated with the poorest prognosis among solid cancers. In the latest NCCN guidelines no clear recommendations have been made regarding LAPC, as chemotherapy and radiotherapy or an experimental treatment in clinical trials are to be considered. IRE which provides cellular apoptosis without any thermal coagulation effect has been previously evaluated and showed promising results (doi: 10.4240/wjgs.v7.i8.138, doi: 10.1136/bmj.h521). This new tumor ablation technique is safe and feasible and could improve local disease control in the LAPC group, nevertheless clinical evaluations are lacking. This study is one of few reporting IRE's benefit regarding overall survival (OS) and progression free survival(PFS) for LAPC compared to a more traditional approach (induction chemotherapy followed by radiotherapy). The authors should be commended for their innovative features.

In my opinion this article should be considered for publication.

1. "Augest" must be written August.
Response: We appreciate the reviewer's advice and this advice is well-taken. The correct writing of “August” has been confirmed and some typos or misprints have been revised in the revised manuscript.

2. In the "methods" section the past tense must be used.
Response: We appreciate the reviewer's advice and this advice is well-taken. According to your suggestion, past tense has been adopted in the "methods" section.

3. Authors should give full term when using an abbreviation for the first time.
Response: We appreciate the reviewer's advice and this advice is well-taken. Full names were given when abbreviation was used for the first time.
4. Too many abbreviations made the reading of the article tedious.

Response: We appreciate the reviewer's advice and this advice is well-taken. The manuscript has been revised and some abbreviations have been deleted when it is feasible.

5. Since Radiotherapy benefits for LAPC are controversial (FFCDSFRO vs MD Anderson) is it opportune to compare IRE to a RT regimen?

Response: We appreciate the reviewer's advice. The current standard of treatment for LAPC is mainly systemic chemotherapy [1]. However, single-agent or combination chemotherapy has been shown to have limited response rates (RR), with little impact on the patient’s survival or quality of life [2]. As a major therapy for cancer, radiotherapy was also adopted as common therapy for LAPC patients [3-5]. The current therapy provided limited success to achieve satisfied prognoses and local control rates, prompting researchers and practitioners to examine novel treatments and to optimize common therapeutic approaches. All patients in the study had received standard chemotherapy, which was recommended for LAPC patients and was believed to provide basic control of disease. The comparisons of IRE and radiotherapy after induction chemotherapy provided useful information in terms of efficacy in LAPC patients and some guidance for clinical practice.

6. Authors should report complications relative to each technique and overall toxicity; indeed the IRE's benefit compared to RT could be explained by differences in toxicity.

Response: We appreciate the reviewer's advice and this advice is well-taken. The complications relative to each technique have been added into the revised manuscript. In the “Result” section, patients of two groups were evaluated for toxicity. The most frequently reported toxicities were hypoalbuminemia and hypotension for patients in IRE group while hematologic adverse events, such as neutropenia, lymphopenia and fatigue, vomiting, and diarrhea were significantly more frequently observed in radiation group. Occurrences of complications were less in patients in IRE group, even though the significances were not significant due to the limited cases. However, muscle weakness occurred significantly more often in the radiation group (10 of 36 patients) (p = 0.006) (Table 4).

7. Is it clinically pertinent to compare IRE to traditional radiotherapy since stereotactic body radiation therapy (SBRT) and intensity-modulated radiotherapy (IMRT) are better tolerated and reported to give better results?
Response: We appreciate the reviewer's advice and this advice is well-taken. LAPC was a deadly disease and patients achieved little improvement in survival from the current treatments. IRE was a novel therapy and might provide help in improving survival of LAPC patients. This study was the first study to show the survival benefit from IRE after the induction chemotherapy, compared with radiation. It was a retrospective study in which patients from August 2015 to August 2017 were included. As the radiation was not the standard treatment for LAPC, the number of LAPC patients who received radiotherapy was relatively small and most of them had received traditional radiotherapy. Although maybe stereotactic body radiation therapy (SBRT) and intensity-modulated radiotherapy (IMRT) might provide a more effective local control for LAPC, they are only be performed in some big cancer center and are not used widely now. The present study aimed to provide the first information regarding to the comparisons of efficacy of IRE and radiotherapy in LAPC patients. However, just as the reviewer pointed out, it was a limitation of this study for the unavailability of comparing the efficacy of IRE and SBRT OR IMRT. Large scale prospective studies with the latest information are being carried out and efficacy of these therapies will be compared and we aim to provide stronger evidence on the possible benefits of IRE certainly in next step of our research project.

Reviewer 2 evaluation

This paper is a well-written research article dealing with the impact of IRE after chemotherapy in patients with LAPC based on the comparison with radiotherapy after chemotherapy. This analysis demonstrated that the OS and PFS in patients with LAPC treated with IRE after chemotherapy was better compared to radiotherapy after chemotherapy, thus IRE was concluded as a better treatment than radiotherapy.

The objective of this study was very curious and interesting, but there are several points that remain unclear.

1. The authors explained the safety and effectiveness of IRE in discussion session, however, complications of IRE were not demonstrated in the study, as the authors mentioned in discussion session as one of limitations. The results and comparison of complications of IRE and radiotherapy should be demonstrated in the manuscript.

Response: We appreciate the reviewer's advice and this advice is well-taken. The complications relative to each technique have been added into the revised manuscript. In the “Result” section, patients of two groups were evaluated for toxicity. The most frequently reported toxicities were hypoalbuminemia and hypotension for patients in IRE group while hematologic adverse events, such as neutropenia, lymphopenia and fatigue, vomiting, and diarrhea were significantly more frequently observed in radiation group. Occurrences of complications were less in patients in
IRE group, even though the significances were not significant due to the limited cases. However, muscle weakness occurred significantly more often in the radiation group (10 of 36 patients) \((p = 0.006)\) (Table 4).

2. In this study, female tends to be a risk factor of LAPC in OS and PFS analyses, however, the proportion of female patients treated with IRE after chemotherapy was higher than that with radiotherapy after chemotherapy. Moreover, The OS and PFS of patients with IRE after chemotherapy were better than those with radiotherapy after chemotherapy. If the authors have any explanations about the association between female and IRE, please add these explanations in the manuscript.

Response: We appreciate the reviewer's advice and this advice is well-taken. According to the suggestion of reviewer, some explanations about the association between gender and IRE were added into the revised manuscript. It was shown that gender was associated with PFS in this study while it was proven to be not an independent prognostic factor for both OS and PFS. Therefore, gender could not predict survival for PDAC patients in this study. Because higher values of C-reactive protein (CRP) were more frequently observed in male patients (16 of 36, 44.4%), compare with female patients (9 of 36, 25.0%) and CRP was a well-known inflammation index, the multicollinearity might contribute to seeming prognostic significance of gender. After multivariate analysis, which could reduce multicollinearity of variables, it was shown that gender was significantly associated with both OS and PFS and male was a risk factor in LAPC patients. This conclusion was consistent with previous studies [6, 7].

Minor comments
1. "with LAPC deemed eligible" should be "with LAPC were deemed eligible" (page 13 line 11).

Response: We appreciate the reviewer's advice and this advice is well-taken. The correct writing has been added in the revised manuscript.

2. "Therefore, there was no a concensus concerning the survival" should be "Therefore, there was no concensus concerning the survival" (page14 line15).

Response: We appreciate the reviewer's advice and this advice is well-taken. The correct writing has been added in the revised manuscript.
Reference


