

Peer Review File

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**Reviewer A**

*Thank you for allowing me to review this interesting manuscript. I do find this work very noteworthy since there is very little published data on this method.*

*First, I recommend having the manuscript worked through by a native English-speaking editor. This would increase the level on the manuscript. The language of the manuscript does not meet the standards of academic publishing.*

Reply: Thank you for your valuable advice. Our manuscript has been proofread and copy edited carefully by a native English speaker with an experience in medical writing.

*I recommend that you try to rethink your manuscript. What do you want to convey to the reader? It does not matter that you cannot conclude anything. Your findings are unique and important to get out. Focus on your findings and portray them systematically.*

Reply: We appreciate the constructive suggestion for our manuscript. We have redrafted our findings in abstract as follow “**Results** The procedure was successful in all cases and no major adverse events were observed. The post procedure imaging studies and serum CA19-9 level were performed 1 month after procedure, showing two patients had decreased lesion sizes and five patients had decreased serum CA19-9 level. Follow-up duration ranged 2 to 12 months. The patient who underwent 8 total sessions of RFA survived 12 months after follow-up and showed increased tumour apparent diffusion coefficient (ADC) value and 20% ablated area inside the tumour. **Conclusion** A multiple-round ablation with optimal RFA energy could be a technically feasible, safe and short-term efficacy option for those patients with unresectable pancreatic cancer.”

Changes in the text: P 3 line 12-20 and P 4 Line 1-2.

*P 2 Line 12-13: Good, clear aim.*

Reply: We appreciate it so much.

*P 2 Line 17: Should this be "one week later"?*

Reply: Thank you very much for your careful review of our manuscript. We have rewritten it as "one week later".

Changes in the text: P 3 Line 10.

*P 3 Line 2-3: Follow up 2 to 12 months. Include them all.*

Reply: Thank you for your suggestion. We have modified this sentence as follow "Follow-up duration ranged 2 to 12 months."

Changes in the text: P 3 Line 12.

*P 3 Line 4-5: The conclusion should answer the full aim. Is it effective?*

Reply: We have redrafted the conclusion as follow "A multiple-round ablation with optimal RFA energy could be a technically feasible, safe and short-term efficacy option for those patients with unresectable pancreatic cancer."

Changes in the text: P 3 Line 15-16.

*P 4 Line 1: Please be consistent in spelling tumor/tumour.*

Reply: We have replaced "tumor" with "tumour" throughout the manuscript.

Changes in the text: P 3 Line 3; P 11 Line 21; and P 15 Line 12,15,16 and 17.

*P 4 Line 11-12: "Promising results has been reported for EUS-RFA in treating pancreatic cancer as a technically feasible and minimally invasive option and a novel future modality (10)." You should note that this is in porcine pancreas.*

Reply: The sentence was not fully appropriate here. We have revised the sentence as follow "Promising results has been reported for EUS-RFA of pancreatic cancer as a technically feasible and minimally invasive option and a novel future modality in a porcine model (10). "

Changes in the text: P 6 Line 2-3.

*P 4-5 Line 21-1: The probe should be described under "Methods", not "Introduction".*

*Is it necessary to write why you have chosen that probe?*

reply: Since the probe and RFA electrode have been described in detail under "Methods" (see P 8 Line 3-5 and 15-17), We agree with your advice and have removed the sentence "In our study, we used a new monopolar probe (Habib™ EUS RFA) that fits better into the EUS needle. The RFA electrode transmitting monopolar RFA energy is the RITA System Generator 1500X. It uses coaxially deployed hooks, which may generate more uniformly spherical thermal lesions" from the Introduction section.

Changes in the text: P 6 Line 14-17.

*P 5 Line 10: Please note at which institution.*

reply: We have added the institution and the sentence now reads, "In the present study, data of eleven patients with unresectable pancreatic cancer referred to EUS-RFA were prospectively collected from Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology between November 2013 and November 2018, and retrospectively analysed."

Changes in the text: P 7 Line 1-5.

*P 6 Line 9: Was the needle introduced through the ventricular wall or duodenum?*

Reply: This is a professional question. Our statement about FNA might be a little bit unclear, so we have redrafted it as follow, "The tip of FNA needle was then positioned at the deepest part of the tumour through the gastric wall or duodenum."

Changes in the text: P 8 Line 8.

*P 7 Line 1-2: "Clinical follow-up was conducted at each other month after the procedure." Please specify what clinical follow-up consist of.*

Reply: We have elaborated on clinical follow-up as follow, "Clinical follow-up (consisting of CA19-9, imaging examination, clinical signs and survival time) was conducted at each other month after the procedure."

Changes in the text: P 9 Line 3-4.

*P 8 Line 14: decreased, not declined.*

Reply: Thanks. We have replaced "declined" with "decreased".

Changes in the text: P 11 Line 7.

*P 8 Line 14-17: Please mention case numbers.*

Reply: We have added the case numbers in this section as follow “In 2 patients (case 3 and case 5) the tumour size decreased, and the serum CA19-9 levels decreased in 5 patients (case 1, case 4, case 5, case 8 and case 9) (Table 2). In one patient (case 3), we observed increased tumour ADC value (Figure 2) and 20% ablated area inside the tumour (Figure 3), indicating a favourable response to cancer therapy.”

Changes in the text: P 11 Line 6-12.

*P 8-9: Line 19-1: Consider leaving this part out.*

Reply: We have leaved this part “After discussing her prognosis and palliative options with her doctor, she declined to receive chemotherapy because of concerns about adverse reactions, but insisted on taking the RFA treatment option” out following your advice.

Changes in the text: P 11 Line 14-16.

*P 9 Line 17: Should say “Barthet et al”, not Marc et al.*

Reply: Thank you. We have replaced “Marc et al” with “Barthet et al”.

Changes in the text: P 12 Line 11-12.

*P 10 Line 7: “Another to be improved is...” Please rephrase.*

Reply: We have rephrased this sentence as follow “Another problem is to achieve complete coagulation necrosis of pancreatic lesions with large diameter.”

Changes in the text: P 13 Line 3-6.

*P 11 Line 12: Not correct to use references here.*

Reply: We have removed the references here according to your suggestion.

Changes in the text: P 14 Line 14-15.

*Discussion: Consider whether your suggestions make sense. You did not see any evidence that a reduced measure of CA19.9 correlate with longer survival after the procedure. But did you investigate this? Can you really suggest that two rounds of*

*ablation are not enough when only two patients received more?*

Reply: Thank you for your valuable comments. This part was not fully appropriate here. We have revised it as follow “We observed case 3 who survived one year after follow-up and showed increased ADC value of DWI and 20% ablated area, indicating survival benefit maybe achieved. It has been reported that the decrease of CA 19–9 during chemotherapy with gemcitabine predicts survival time in patients with advanced pancreatic cancer (23). However, cases in our study such as case 4 and case 5 who were found died due to metastasis although had reduced CA19-9 value after procedure, it seems that EUS-RFA did not provide a survival benefit. In the future, a case series study is required to confirm our results.”

Reference 23: Halm U, Schumann T, Schiefke I, et al. Decrease of CA 19-9 during chemotherapy with gemcitabine predicts survival time in patients with advanced pancreatic cancer. Br J Cancer. 2000;82(5):1013-6.

Changes in the text: P 15 Line2-10.

*Interesting thoughts about immune response.*

Reply: We appreciate your recognition of our thoughts so much.

*Conclusion: You should answer your aim. P5 L5: “...and evaluated the technical feasibility, safety and efficacy”*

Reply: We have redrafted the conclusion section as follow “The present case series showed that a multiple-round ablation with optimal RF energy is feasible, safe and short-term efficacy for patients with locally advanced pancreatic cancer. However, the long-term efficacy of this novel treatment method should be further assessed in properly designed studies.”

Changes in the text: P 16 Line 8-21 and P 17 line 1-2.

*Your study limitations should be presented under “Discussion”.*

Reply: Thank you for your suggestion. We have removed this information from the “Conclusions” and added this part in the end of the “Discussion” as follow “Our study presents the following limitations: a small cohort of patients, a short follow-up

period, and their disease was heterogeneous. Moreover, given the short-time interval in analysis and the discontinuing after two round RFA treatments in most patients, it is still not possible to deduce any conclusion regarding the improvement in the survival rate after RFA procedure.”

Changes in the text: P 16 Line 2-6 and 17-21; and P 17 line 1.

*Table 2.: Is the size measured on CT, MRI or EUS?*

Reply: Since only CT were performed both before the EUS-RFA and after the EUS-RFA in all patients, we chose the size measured on CT to evaluate the technical efficacy. We have noted it on Table 2.

Changes in the text: Table 2.

**Reviewer B**

*Dear Authors, I read with interest your paper and al appreciate your efforts, although I see many limitations in your retrospective study.*

*Procedures have been performed along a large period of time, moreover results judged in terms of ca19.9 level changes may be insufficient to judge the efficiency of the procedure. Evaluation of ablated area percentage might be a better option. In conclusion I think your paper doesn't offer much information in comparison with recent literature (for example "EUS-guided Radiofrequency Ablation (EUS-RFA) of Solid Pancreatic Neoplasm Using an 18-gauge Needle Electrode: Feasibility, Safety, and Technical Success. Crinò SF, D'Onofrio M, Bernardoni L, Frulloni L, Iannelli M, Malleo G, Paiella S, Larghi A, Gabbrielli A. J Gastrointestin Liver Dis. 2018 Mar;27(1):67-72. doi: 10.15403/jgld.2014.1121.271.eus)*

Reply: Thank you very much for your professional review of our study. We have added ablated area percentage to judge the efficiency of the procedure according to your suggestion and this meaningful literature.

Given that this was a retrospective preliminary study, we evaluated main outcomes, including the technical feasibility, safety and efficacy, measured by the tumour size, the tumour apparent diffusion coefficient (ADC) value of MRI- DWI, CA19-9 level and ablated area percentage. The results showed that the procedure was successful in all cases and no major adverse events were observed. The post procedure imaging studies and serum CA19-9 level showed two patients had decreased lesion sizes and

five patients had decreased serum CA19-9 level. Follow-up duration ranged 2 to 12 months. One patient who underwent 8 total sessions of RFA survived 12 months after follow-up and showed increased tumour ADC value and 20% ablated area inside the tumour. The present case series demonstrated that a multiple-round ablation with optimal RF energy is feasible, safe and short-term efficacy for patients with locally advanced pancreatic cancer.

Changes in the text: P 3 line 13-19; P 11 Line 3-21; and P14 line 13-15.