

We thank the Editor and the Reviewer for their interesting observations and constructive comments. In the following, we report our answers (in bold face) to specific comments. On their basis we have amended the manuscript using changes track. We are confident that now the manuscript will encounter their satisfaction.

Summary Granata et al. reviewed the local ablation therapy for pancreatic tumors. Although the manuscript well described about current situation and future perspectives of the local ablation therapy for pancreatic tumors, there are some points to be revised.

Major points

[Introduction]

- 1) Page 3 line 71; The latest NCCN guidelines for pancreatic adenocarcinoma was published in 2021, as version 2. Please refer this latest version of the NCC guideline. (The reference No.2; http://webdefence.global.blackspider.com/urlwrap/?q=AXicFcc7DsIwDABQV-I8TosQAibYmLkACqYfizaObleq52VnYwfe9uAEr1UF5Q2g41I3NzR94hR5JEmuMiLJB M36cn7Ufqqb7W6_AcWuGMmRzdmLi5dJIDFFZifBPdshhHmeMREIFO1DVulaM5YUR wt5WIyJY7r2_927kGMibaMz4a8A8IEKvjVQNf4&Z)

We modified as suggested

- 2) Page 3 line 72; the definition of “Cure rate” is unclear. The reference used in this sentence discussed about the median overall survival of the FOLFIRINOX therapy. Please reconsider this sentence.

We modified as suggested

- 3) Page 4 line 74; For the patients with germline BRCA 1/2 mutations, the olaparib was recommended for the patients who have not progressed during first-line platinum-based chemotherapy. It is mentioned in the latest NCCN guidelines. Please reconsider the sentence that the gemcitabine/cisplatin is used for the patients with germline BRCA 1/2 mutations as a first-line chemotherapy.

We modified as suggested according to latest NCCN guidelines

- 4) Page 3 line 75-77; Please show the evidence of the following sentence, as it may lead readers misunderstanding for the systemic chemotherapy for the advanced pancreatic cancer patients. “Despite the recent introduction of novel chemotherapeutic schemes, these treatments still relate with a poor long-term survival and significant ad interim systemic complications”.

We modified the sentence

[Methods]

- 1) Page 4-5; In the inclusion criteria, please refer which study designs were included in this review (i.e. Retrospective analysis, Case series/reports, Prospective cohort study). It may affect the impact of this review manuscript.

We modified as suggested

- 2) Page 4-5; In the inclusion/exclusion criteria, which pathological type of the tumor was included or excluded? Please refer the pathological type included in this study.

We modified as suggested

[Results]

- 1) Page 5 line 124; the term “FOLFIRINOX” therapy is not a common term. It may indicate 5-FU based regimen (Wang-Gillam et al. Lancet. 2016 Feb 6;387(10018):545-557. doi: 10.1016/S0140-6736(15)00986-1.). Please reconsider the term.

We modified as suggested

[Discussion; Ablation Techniques- Physical Principles]

- 1) Page 6 line 139-145; the RFA system has both monopolar and bipolar system. The bipolar system of the RFA can reduce the heat sink effect and lower pancreatic injury (Testoni et al. Endosc Ultrasound. 2020 Mar-Apr; 9(2): 83–100. Published online 2020 Apr 15. doi: 10.4103/eus.eus_74_19). Please consider to add this point of view in the main text.

We modified as suggested

[Discussion; Clinical study Radiofrequency Ablation]

- 1) Page 7 line 173-177; the reference guideline for the staging is not clear. Please cite the guidelines used for staging. If the multiple staging methods were used, please replace the term stage-III as “locally advanced pancreatic cancer” and stage-IV as “metastatic pancreatic cancer”.

We modified as suggested

- 2) Page 8 line 178-179; From the reference No. 43 and 44, it seems that there is not enough evidence of RFA for the upfront treatment, although the RFA may have a potential to be the one. Please reconsider the main text.

We introduced the reference 9 in with Paiella et al suggested RFA as an upfront treatment

- 3) Page 9 line 219-222; It seems that the term “dimension reduction” is not commonly used. Please describe what the dimension reduction indicates.

We modified as suggested introducing the reference od RECIST 1.1 criteria [15]

[Discussion; Microwave Ablation]

1) The complication rates of the MWA were varied among the studies retrieved in this manuscript. It may due to the heterogeneity of the studies retrieved. Please discuss this possibility. If the heterogeneity is observed, please describe specific information about the heterogeneity.

We modified as suggested adding the sentence:

However, the complication rates of the MWA were varied among the assessed studies. It might due to the heterogeneity and the simple size of the studies assessed. In fact, Carrafiello et al [59] treated 10 unrespectable head pancreatic adenocarcinomas, Ierardi et al [60] treated five head pancreatic locally advanced cancer and Vogl et al [61] treated 22 patients: in 17 patients (77.3%) the tumour was in the pancreatic head and in 5 (22.7%) in the pancreatic tail.

[Discussion; Irreversible electroporation]

1) Page 11 line 174; It seems that the suitable target area should be 3-3.5 cm in diameter, not “mm”. Please reconsider the text.

We modified as suggested

2) Page 12 line 282-284; Reference No.6 reported a variety of complications. Please describe which is the main complications and which is the minor complications.

We modified as suggested

[Discussion; Comments and future prospectives]

1) Page 16 line 385; There is a discussion whether we can consider that the ablation therapies for pancreatic tumor as a “safe technique” in terms of post-procedural complications (Linecker et al. Dig Surg. 2016;33(4):351-9. doi: 10.1159/000445021. Epub 2016 May 25). Please describe specifically the reason why the authors considered the technique as safe, since some complications are decrease the patients’ quality of life.

We modified as suggested and introduced the reference as 69

Minor points

[Results]

1) Page 5 line 126: It seems there is mistyping. I think “simple size” should be “sample size”. Page 5-6 lin126-133; The term “mayor complication rates” should be “major complication rates”.

We modified as suggested

Editor

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.

We revised as required

Please provide the author contributions

We added as required

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.

We added as required

Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. For PMID and DOI numbers of references from English-language journals, please ensure there is a space between the PMID and DOI numbers in the square brackets. Please revise throughout

We added as required

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Only original figures are submitted.