Peer Review File

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Review comments

Reviewer 1
Comment 1
Title. The title reflects the main subject of the manuscript.

Comment 2
Abstract. The abstract summarizes and reflects the work described in the manuscript in a short and clear manner with summary of the aims, methods, findings. However, I suggest pointing out lacking prospective studies and that the definitive role of radiation in MPC is to be determined in the future prospectively designed studies.

Reply 2: Thank you for this suggestion. I have added a phrase in the Key Content and Findings section to specify that "prospectively designed studies are currently lacking" in the oligometastatic setting. I have also added that "further prospective study is required" to the final sentence of the Conclusions.

Comment 3
Key words. The key words reflect the focus of the manuscript.

Comment 4
Background. It clearly summarizes the current state of the topic. It clearly defines the aim of the study and this is consistent with the rest of the manuscript. However, I miss addressing the limitations of current knowledge in this field. The research question is appropriate for clinicians dealing with pancreatic cancer patients.

Reply 4: We appreciate the reviewer's feedback. Based on these comments, we have added to the introduction paragraph 1, last sentence: "The question remains …yet to be determined." This statement serves to underscore that this subject material is not yet settled, and in the conclusion, we underscore the limitations of the current evidence base.

Comment 5
Methods. Though I respect the authors' judgment the clarifying of the articles, selection in the presented work would be recommended. Although I appreciate the retrospective nature and limited number of studies, I would suggest organizing of presented studies in the table. I would recommend going through references, e.g. reference 7 is not covering for statement.

Reply 5: We appreciate the reviewer's thoughtful comments. We were guided by the journal's narrative review checklist which directs the authors to "Specify the process for identifying the literature search (eg years considered, language, publication status,study design, and databases of coverage)." While we included several of these elements in the initial draft, to better comply with these terms, we have revised the Methods sentence 2 to say "Retrospective and prospective

studies available in the English language that reported outcomes for patients with metastatic pancreatic cancer who received radiotherapy were reviewed and included based on the authors' judgment." Regarding the references, we have re-arranged and added two additional references to support the statement regarding the indication of palliative radiotherapy in pancreatic cancer in lines 95-100"Potential symptoms of…byproduct of palliative radiotherapy." We have also included two tables summarizing the studies discussed for SBRT for local palliation of MPC and metastasis-directed therapy in OMPC.

Comment 6
The main text section is appropriately broken down to smaller sub-parts. The limitations of the studies and bias of interpretation should be mentioned.

Reply 6: Thank you. To address these concerns, please see the added statements in lines 161-164 "These studies both underscore…a better outcome." and lines 174-176 "These trials will provide…decisions in MPC." Regarding OMPC, please see existing sentence in lines 191-192 "Prospective data specifically…OMPC are lacking." And lines 250-252 "Prospective studies are required…oligometastatic pancreatic cancer."

Comment 7
Overall, I agree with the conclusions from the Authors regarding the role of radiation in pain management and possibility for dose escalation with use of modern radiotherapy techniques. Nevertheless, I recommend the Authors to stress the need to run randomized trials including quality of life and cost-effective analyses. The future directions of the topic described in this manuscript should be proposed. Authors can be clear about the questions/issues that remain to be solved.

Thank you. We have added a sentence to the conclusion stating that "Randomized trials assessing quality of life and cost-effectiveness of radiotherapy would be beneficial to further understand the value of radiotherapy in the context of MPC."

Reviewer 2

This narrative review addresses the evolving role of radiotherapy for metastatic pancreatic cancer (MPC). Importantly, the use of radiotherapy in the setting of MPC is a generally underdeveloped research area that merits further investigation, most notably within the context of metastasisdirected and immune-adjuvant approaches. The review is very well written, clearly presented, and handily organized into palliative, metastasis-directed, and immune-adjuvant subsections. The authors do an excellent job of featuring studies that are most relevant and impactful to these topics, notably the pilot study by Hammer et al. demonstrating palliative efficacy in the setting of celiac plexopathy, and the retrospective analysis by Elamir et al. highlighting the survival benefits of metastasis-directed radiotherapy over chemotherapy alone. Although the "SBRT and Immunotherapy in MPC" section is lacking in scope relative to others, it is of note that this is an emerging concept that remains highly understudied. I support the acceptance of this article upon

the minor revisions detailed below:

Comment 1
Line 82: Please define the “metastatic pancreatic cancer” abbreviation (MPC) upon introduction.

Reply 1: Thank you, please see line 79 of the introduction for addition of the abbreviation.

Comment 2
Lines 235-8: While discussing the induction of an immune response by radiotherapy, the statement “increased tumor antigen presentation resulting in increased CD8+ T cell activation and subsequent immunogenic cell death” is somewhat misleading. Radiotherapy can indeed augment immunogenic cell death (ICD) by way of necrosis/necroptosis and antigen presentation via increased HLA expression, however, the two effects are most accurately represented as occurring independently (albeit related). As written, this statement seems to suggest that T cell activation resulting from enhanced antigen presentation leads to ICD, when in fact ICD is most generally recognized as a key driver of T cell activation via release of neoantigens and dangerassociated molecular patterns (DAMPS). Please revise.

Reply 2: Thank you for bringing this to our attention. We have revised the sentence as follows (lines 257-261): “The reasons for this lack of efficacy may relate to the immunosuppressive tumor microenvironment in pancreatic cancer (37,38). Radiation therapy can promote an immunologic response via multiple mechanisms, including induction of immunogenic cell death(39), tumor antigen presentation via increased expression (40,41), and promotion of T-cell homing to the tumor bed (42–44)..”

Comment 3
Lines 241-2: The statement that current clinical studies have evaluated the safety but not the efficacy of SBRT in addition to immune checkpoint inhibition is partially untrue. Recent work by Parikh et al. (PMID: 35122060) demonstrated the modest efficacy of radiotherapy in enhancing the effects of immunotherapy in microsatellite stable (MSS) MPC, and these findings should be discussed. Moreover, the section could further benefit by emphasizing consideration for tumor microsatellite stability/instability during the design and interpretation of SBRT plus immunotherapy clinical research.

Reply 3: Thank you for this suggestion, a brief discussion has been added to lines 289-294 (“Mismatch repair deficiency, which is a positive…in patients with MPC.”) We have also added additional efficacy signals reported from the CheckPAC trial and the trial by Xie and colleagues in lines 264-289.

Comment 4
The “SBRT and Immunotherapy” section would benefit from a brief discussion regarding the impact of chemotherapy and radiotherapy dose/schedule on the development of an anti-tumor immune response. A central challenge of combining cytotoxic and immune therapies is timing the treatments to maximize tumor damage while limiting residual toxicity to the subsequent immune response.

Reply 4: Thank you for this suggestion, a brief discussion has been added (“Questions also remain regarding…conjunction with radiotherapy”) in lines 294-297, with a focus on factors to

consider regarding timing of radiotherapy as it pertains to both the study by Parikh et al and preclinical studies.