Peer Review File

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Reviewer A

The paper provides an excellent overview of the current status of clinical evidence for this interesting concept of the abscopal effect. The problem remains to really prove this in patients so that this will not remain just an assumption.

Reply: We thank the reviewer for their evaluation of our submitted manuscript, No changes were made in response to reviewer comments

Reviewer B

This paper is well-structured and consistent from the introduction to the conclusion. The writing is clear and concise. Additionally, there are few reports on the abscopal effect in digestive cancers, and I have not seen any reports that are organized by organ as in this study. Therefore, this paper is very valuable as it summarizes the current situation of the abscopal effect in digestive cancers, which is a hot topic, in an easy-to-understand way. Based on these factors, I recommend that the paper be accepted for publication.

Reply: We thank the reviewer for their evaluation of our submitted manuscript, No changes were made in response to reviewer comments

Reviewer C

The manuscript "Harnessing the Abscopal Effect for Gastrointestinal Malignancies in the Era of Immunotherapy" is a comprehensive review of the benefits of combined radioimmunotherapies.

The manuscript is well written, logically structured and the figure as well as the table with clinical data are meaningful additions.

Comment 1: Some proofreading might help to further increase readability.
Reply 1: We thank the reviewers for their evaluation of our submitted manuscript. We have proofread the manuscript and have made minor grammatical revisions to the final version. The overall content of the final manuscript has not been significantly changed beyond what was necessary to improve readability. Please see the listed changes below. Changes have also been tracked in the revised manuscript.
Notable changes in text:

1. Lines 44-47: “There has thus been emerging interest in determining the optimal treatment strategy for the delivery of immunotherapy in combination with traditional therapies. In this regard, a growing number of preclinical and clinical studies have suggested that

combining radiation therapy (RT) with immunotherapy may work synergistically to improve treatment response through amplification of the abscopal effect."

2. Lines 56-58: "Gastrointestinal (GI) cancers such as esophageal, gastric, pancreatic, hepatobiliary and colorectal cancers (CRCs) account for approximately 20% of newly diagnosed cancers and a substantial proportion of all cancer-related deaths in the United States each year"
3. Line 69: "Over the past decade the rapid emergence and availability of targeted immunotherapies, especially immune checkpoint blockade (ICB) therapies have dramatically transformed the treatment landscape for solid tumor oncology"
4. Lines 71-76: "Unlike traditional chemotherapy or RT, which directly kill cancer cells, immunotherapy harnesses the host's preexisting immune system to eradicate tumor cells by activating immune cell anti-tumor activity. For GI malignancies, immunotherapies have likewise gained increasing attention over the past several years. ICB, vaccine therapies, and adoptive cell transfer therapies have particularly demonstrated promising clinical activity for a subset of patients with metastatic GI disease."
5. Lines 78-81: "In this regard, there is growing evidence to suggest the immunomodulatory function of RT, and its potential to work synergistically with immunotherapy through a phenomenon known as the abscopal effect. In this review we provide an overview of current evidence, recent advances, and future directions for the potential combinatory role of immunotherapy with low-dose radiation therapy in GI malignancies."
6. Lines 115-119: "This is process is additionally mediated by the increased translocation of calreticulin and other ligands that help promote DC phagocytosis, as well as upregulated expression of MHC Class I (16,17). There is further evidence to suggest that radiation therapy may help to expand and diversify the tumor-directed TCR repertoire, thereby increasing the likelihood of tumor-antigen recognition"
7. Line 121: "Low to moderate doses of radiation have also been shown to modulate the inflammatory milieu"
8. Lines 140-144: "in certain solid malignancies (30). Nevertheless, the expression of PD-L1 on tumor cells has been shown to be a useful biomarker for predicting response to ICB therapy (31). This provides additional rationale for combining PD-1/PD-L1 inhibitors with radiotherapy.
9. Lines 168-171: "previously received radiotherapy had longer progression-free survival (PFS) and overall survival (OS) with pembrolizumab, an anti-PD1 inhibitor, than those who did not receive previous radiotherapy (35,36). Similar findings have also been observed when ipilimumab, an anti CTLA-4 inhibitor,"
10. Line 183-193 "While early stage or locally advanced esophageal cancers can often be cured with endoscopic resection or esophagectomy, more advanced stage disease requires additional systemic chemotherapy with or without radiation therapy for suppression of local tumor growth and alleviation of dysphagia (46,47). More recently, immune checkpoint inhibitors have been incorporated into the management of patients with upper GI cancers (48)."