

Peer Review File

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Reviewer A

Comments:

The present manuscript is a comprehensive review on the clinical trials about the combination between radiotherapy and ICIs in lung cancers. The manuscript is potentially interesting and depicts an important new scenario in the treatment of these neoplasms. However, some additional work is required in order to reach publication priority.

On these bases the following major concerns should be raised:

1) The authors should clearly state the biological basis of the combination between radiotherapy and ICIs in the treatment of lung cancer. I suggest also to add a picture elucidating the role of radiotherapy in sensitizing tumor cells to the ICIs. Moreover, more relevance should be given at the so-called "abscopal effect".

Author Response: Thank you for your comment. The entire section of the manuscript, "The Combination of Radiation Therapy and Immunotherapy" was devoted to defining the biological basis of the combination between radiotherapy and ICIs in the treatment of lung cancer. While this section was already a robust three paragraphs, we have expanded this section, given additional biological bases and mechanisms of synergy, added additional references including some recent reports that have included detailed figures showing the mechanism of interaction between radiation therapy and immunotherapy. We have also expanded the abscopal effect discussion to be an entire paragraph within "The Combination of Radiation Therapy and Immunotherapy" section.

2) The authors should clearly state the reasons that they suggest at the basis of the failure of the available clinical trials in demonstrating a definitive effect to the combination of radiotherapy with ICIs. Moreover, some preclinical work has to be cited in this regard. An example is the following recent manuscript:

PMID: 30841910.

Author Response: Our entire manuscript is dedicated to discussing the potential rationale for combining radiation therapy with ICIs, the preclinical and clinical data that are currently available, and the ongoing trials that are further assessing and will better define the combination therapy. Preclinical data are discussed in the now expanded “The Combination of Radiation Therapy and Immunotherapy” section. Given the rapidly growing clinical evidence and the significant increase in active trials, a comprehensive review dedicated to preclinical evidence is beyond the scope of this review and has been reported at length by others previously. Thank you for pointing out this helpful reference, though. It has been added to our preclinical section of the manuscript.

3) The authors should give more details on the predictive biomarkers of response to ICIs in lung cancers citing and appropriately discussing the following recent manuscripts adding a dedicated paragraph: PMID: 30680606, PMID: 32272498, PMID: 29658845, PMID: 29731394 and others. Some insight on HLA haplotype and response to ICIs in lung cancer should also be given citing the following recent paper: PMID: 32554614. Finally, the authors should cite "radiomics" as a new way to predict response to ICIs citing the following manuscript: PMID: 32554614.

Author Response: We have a discussion in the “Future Directions” section on the possibility of utilizing biomarkers that predict response to immunotherapy to predict possible response to the combination of immunotherapy and radiation, as well as the use of class I and II HLA allele characterization to predict response to therapy. All five of the provided references have been added. Additionally, we added a discussion on radiomics in the “Future Directions” section. We believe the reviewer inadvertently provided the increased reference that he/she wanted us to cite, but we have added new references for this.

4) A paragraph focusing on the possible combination of chemotherapy with ICIs and radiotherapy in the treatment of lung cancer should be added (with a related and connected table) citing some relevant recent manuscripts such as the following: PMID: 29221287 and PMID: 29100279.

Author Response: The first paper does not include radiation therapy and the second paper does not include immunotherapy. While these are both very interesting works that have implications for immune response, these works are well outside the scope of a paper solely dedicated to combining radiation therapy with immunotherapy and specifically immune checkpoint inhibitors.

5) Some misreadings in the text should be carefully corrected.

Author Response: We have reviewed the entire manuscript and corrections have been made, where necessary.

Reviewer B

Comments:

It is well written and covers most of the relevant areas and literature within this topic.

- I would encourage the authors to have a section on clinical risk factors for immune related complications when radiation is combined with immunotherapy. The challenge going forward with combined approach is recognizing which patients are high risk for complications, such as pneumonitis (eg patients with significant chronic lung diseases).

Author Response: We appreciate the feedback and have included a new section dedicated to "Radiation and Immunotherapy Toxicity," with a focus on lung toxicities. Pneumonitis is discussed at length throughout this new section.

- The impact of extra thoracic radiotherapy is also of interest. This is briefly stated in the manuscript. A paragraph on this would be greatly appreciated.

Perhaps consider citing some of the well-established literature on combined immunotherapy and radiation in other malignancies. Along the same lines, please comment on the dose of radiation needed for abscopal effects.

Author Response: as discussed for Reviewer A, we have added a paragraph dedicated to the abscopal effect, and we were able to cite lung and thoracic-specific literature for this. We have also added mention on the benefits of SBRT over conventionally fractionated radiotherapy for achieving the abscopal effect and that the most optimal dose fractionation regimen is current an area of active investigation.

- Please discuss if there is a difference in the efficacy between different immunotherapy agents when combined with radiation (ie: durvalumab vs pembrolizumab vs nivolumab..).

Author Response: While most of our discussion in the original manuscript submission was on optimizing variables of dosing, fractionation, timing, and modality of radiation to be used in combination with immunotherapy, we have added a discussion on the variables of specific immune checkpoint inhibitors and the different types of immunotherapies and how these can impact the synergistic effect with radiation therapy in the "Future Directions" section.

- Please review the recent publications on combined nivolumab and radiation in advanced disease.

Author Response: Over the past 2 years, we have identified six relatively impactful reports of combining nivolumab with radiation therapy for locally advanced or metastatic lung cancer as follows:

- PMID 32770608
- PMID 32567218
- PMID 31703637
- PMID 31200833

- PMID 30888716
- PMID 30452687

We are unsure which report you are specifically referring to. The first of those papers focuses on ICI resistance, the second is a case study, the third is a trial in progress report without data, the fourth we already cite and discuss (Peters et al, which was formerly reference #54 and is now renumbered), and the sixth is only 6 total patients. So presumably you are referring to the fifth paper, and we have added a detailed discussion of this important paper and the references to the revised manuscript.