

Peer Review File

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Reviewer A

Comment 1: This is a review article about proton beam therapy for malignancies with palliative intent. The authors presented the efficacy and safety of proton beam therapy in palliative care comparing with conventional radiation therapy with photons. It is interesting and well written. However, it is doubtful whether proton beam therapy should be greatly recommended for palliative care instead of conventional irradiation. Indeed, it is theoretically beneficial to some patients, but it is a waste of medical resources for most patients and patients to whom proton beam therapy shows the definite advantage are extremely limited. Advanced radiation techniques with photons, including intensity-modulated radiation therapy, have recently been introduced to many developed countries. From the viewpoint of cost, such treatment options may be more reasonable for palliative irradiation. Proton beam therapy is considered to prove its merits in the second or more courses of radiation therapy for patients with recurrences with curative intent rather than palliative intent.

Reply 1: Thank you for this insightful comment. We agree that most patients receiving palliative radiation therapy are treated as well with photon therapy relative to proton therapy, and with less cost for photon therapy. There are select patients, however, that can have the potential for toxicity reductions or better preservation of quality of life when receiving proton therapy in the palliative setting, and those are the patients for which this manuscript focuses. We have made this point more clear in the revised manuscript. We have also included a discussion on cost effectiveness in the Discussion section

Reviewer B

The authors assess the potential utility of proton therapy delivered to a number of cancers in the palliative setting. This is a very well written paper of interest to the Journal's readership. I have however major concerns:

General comment:

Comment 1: It would be advisable to rethink the orders of the sections. If queried, the majority of radiation oncologists would probably think that PT in the palliative setting would be more important for H&N or lung cancers than for CSI. The choice of describing the palliative treatments utilizing protons in an pseudo anatomical, as opposed to clinical relevance, order could be challenged.

Reply 1: Thank you for this helpful comment. We have reordered the manuscript to start with lung and head and neck, with clinical relevance driving the revised ordering.

Comment 2: It is unclear to the reviewer why table 2 only list some cancers that are detailed in textual information. Please modify.

Reply 2: This table highlights benefits of proton beam therapy specifically in the reirradiation setting across disease sites mentioned in the paper. The few other sites not listed in this table but included in the paper (liver and leptomeningeal disease) did not include studies detailing proton therapy in the reirradiation setting.

Specific comment:

Comment 3: Abstract, line 38: ease of administration: there is no evidence that proton therapy is less easy to administer than photon therapy for metastatic disease. Please re-word.

Reply 3: We have removed “*ease of administration*” from this line.

Comment 4: Introduction, line 59: the statement ‘less scatter and a sharper lateral beam distribution’ is debatable, at least for PBS: at certain (low) energy range, lateral scatter is increased when compared to photon therapy. Please re-word.

Reply 4: Changed to “*which can result* in less scatter and a sharper lateral beam distribution.”

Comment 5: Introduction, line 67: it is probably an over-statement to list the decrease of secondary tumors as an advantage for PT for metastatic disease. Please re-word.

Reply 6: This is an excellent point. We have removed “secondary cancers.” This line now reads: “... 2) *decreased integral dose (or exposure to low dose radiation) to adjacent normal tissues, potentially reducing the risks of subacute and late toxicities.*”

Comment 6: LMD, line 109. It is unclear to the reviewer if this review encompass adult only studies. This should be clearly mentioned in the paper. For instance, LMD is very common in pediatric brain tumors, not limited to ATRT, ependymoma or medulloblastoma.

Reply 6: This review only focuses on the adult patient population. We have clarified that in the revised manuscript both in the abstract (“among adults”) and specifically in this LMD section that now states, “*In a 2021 systematic review of 13 retrospective studies investigating the use of CSI for LMD in adult patients 18 years of age or older...*”

Comment 7: Brain mets, lines 176: the authors should also acknowledge that the current trend in the oncology community is to treat selected BM patients with targeted agents.

Reply 7: We have added the following line as well as the appropriate citations: “*In the last decade, there have been a number of immunotherapy options and targeted therapies approved by the FDA that have significant blood-brain barrier activity. As such, these drugs have been incorporated into the treatment paradigm for brain metastases.*”

Comment 8: Brain mets, lines 188: it is unlikely that proton SRS will reduce the risk of brain necrosis, as this event usually occur in the brain irradiated with high-dose radiation (i.e. in the metastatic lesion initially treated). If anything, pSRS may be associated with an increase risk of brain necrosis due to RBE issues (see the Bloomington data). Please re-word.

Reply 8: We have discussed and cited several studies that support proton therapy potentially being associated with a decreased risk of radionecrosis. However, we have softened the language throughout this section, and we conclude this section saying that more data are needed to determine if there is significant benefit to proton therapy for this patient population.

Comment 9: Brain mets, lines 193: more common side-effects of steroids are diabetes, weight increase and mood issues.

Reply 9: We added “*weight gain, hyperglycemia and mood issues*” to the list of potential side effects.

Comment 10: Brain mets, line 227: it would be advisable that this para. is inserted earlier in the Brain metastasis section: first, the authors should mentioned comparative planning studies, then series with clinical results. Please modify.

Reply 10: Thank you for this suggestion. We have restructured this section to include this study first followed by more clinically based studies.

Reviewer C

This is a timely and impactful report of the use of an advanced modality, namely proton therapy, to treat advanced malignancies. While most of the literature to date with proton therapy has been for early stage and locally advanced disease, this is a novel report of the role this modality can play for advanced, metastatic, and recurrent cancers. It is very comprehensive and well written. I recommend accepted. I do have two recommendations that should be considered first.

Comment 1. The Conclusion section is very long. All of the content is appropriate, but perhaps this should be re-termed Future Directions or something else, since I usually think of conclusions as a single paragraph.

Reply 1: Thank you for this helpful suggestion. We have now divided this section further into *Future Directions* and *Conclusions*, as recommended.

Comment 2. The authors do not discuss FLASH, which is perhaps the hottest topic in radiation oncology right now, and the JAMA Oncology used proton therapy to deliver FLASH in bone metastases patients. The authors should add a paragraph discussing the role of protons for FLASH in light of stage IV bone metastases completing and ongoing trials.

Reply 2: This is a very good point. Please see the newly added paragraph detailing proton FLASH radiation therapy in the Future Directions section.