

Peer Review File

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Reviewer 1

Comment 1: The authors investigated proton CSI reported patient reported outcomes in their phase I study (Yang et al. Neuro Oncology 2021) using MDASI-BT and MDASI-SP. It may be important to include as an example to encourage all investigators to utilize tools to assess patient's symptoms and quality of life. Looking at the protocol for their Phase II study included with their JCO publication, MDASI-BT and MDASI-SP were included again as a secondary endpoint as well as neurocognitive testing. These results should be anticipated with their future publications I assume.

Reply 1: We have changed our manuscript accordingly and cited the phase 1 study by Yang et al.

Changes in the text:

page 11, line 11-15: We added “HRQoL was not reported as one of the endpoints, but the assessment of patient reported outcome using the MD Anderson Symptom Inventory for Brain Tumor (MDASI-BT) and MD Anderson Symptom Inventory for Spinal Tumor (MDASI-SP) were the secondary objectives in the protocol of this phase 2 trial, and they have been reported in the result of the phase 1b trial by Yang et al. (25).”

page 23, line 6-9: We added “Until a dedicated tool to measure HRQoL outcomes in LMD has been developed, investigators should be encouraged to utilize tools that cover as much relevant domains for LMD patients as possible, such as the MDASI-BT, MDASI-SP, EORTC QLQ-BN20, or other tools.”

Comment 2: One of the most important knowledge gap in all these trials is the sequencing of multidisciplinary treatments for LMD. LMD is a true multidisciplinary disease that requires multiple modalities though there is a lack of knowledge in terms of how to sequence radiation, systemic therapy, IT therapy etc. This should be investigated and accounted for in the ongoing studies. It may be worthwhile highlighting this.

Reply 2: We have added the following to the “knowledge gap”.

Changes in the text: page 23 line 11-15: “Fourth, the optimal sequence of treatment for LMD remains unknown. Multi-disciplinary collaboration is critical to manage patients with LMD. Most of the studies included in this review focused on specific interventions, such as radiation, systemic therapy or intrathecal therapy. There is limited evidence to date on how to sequence these treatment modalities to achieve the best outcome.”

Reviewer 2

Comment 1: Page 2: The authors indicate that 38 trials met the initial search criteria, but only 19 were selected for detailed review. In the methods it explains how they got to the 19, but would also be helpful to briefly state in the abstract.

Reply 1: We have added the following to our abstract, and simplified the remaining parts of the abstract to keep it within the desired length.

Changes in the text: page 3, line 15-16: We added “Most of the studies that were not selected for discussion focused on biomarker-driven interventions.”

Comment 2: Page 3: I wouldn’t necessarily say the use of WBRT is declining, as it is still certainly utilized for LMD, although of course it has its drawbacks. Would reword this sentence.

Reply 2: We have reworded this sentence accordingly.

Changes in the text: page 5, line 25-26: We changed it to “Whole brain radiotherapy has only modest benefits in this patient population.”

Comment 3: Page 3: Please cite which narrative methods you are utilizing and reference these.

Reply 3: We have added the following to our Methods section

Changes in the text: page 7, line 21-22: The general framework and methodology of this narrative review followed the recommendation by Ferrari (11).

Comment 4: Some of these studies are just listed as enrolling while others are completed, is that correct? Would clarify this also on page 4 so it is more clear to readers why some have results and some just descriptions of the study.

Reply 4: Yes. We have added the following to our Results section.

Changes in the text: page 8, line 21-23: “Some of the studies included were still enrolling, whereas others had their preliminary results published. Our review discussed the methodology of these studies, as well as the early results whenever they were available.”

Comment 5: In some sections, the authors provide comment/perspective on the study, and other ones less so. Would be helpful to add comment/perspective on all trials if possible.

Reply 5: We have added the following comment to the studies on intrathecal checkpoint inhibitor, while maintaining the balance between the depth and breadth of coverage.

Changes in the text: page 18, line 25 to page 16, line 3: We added “As the use of intravenous checkpoint inhibitors is already part of the standard treatment in many types of cancer (71), studies on the combined use of intravenous and intrathecal checkpoint inhibitors might be more clinically relevant than those which used intrathecal checkpoint inhibitors alone.”

Comment 6: What is the source for this checklist? Please cite.

Reply 6: The Narrative Review Checklist is downloaded from the website of the Annals

of Palliative Medicine, as part of the requirement for submission of narrative review articles.

Comment 7: There are a number of grammatical typos throughout. Please check.

Reply 7: The following changes were made.

Changes in the text: page 8, line 18: “remaning” was changed to “remaining”. page 22, line 24: “MDASAI-BT” was changed to “MDASI-BT”.