Peer review file

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Reviewer A

Comment 1: Too vague
Reply 1: We re-wrote the article more concrete.
Change in the text: Please see all.

Comment 2: Incidence of hippocampal metasasis Low please reference Here.
Reply 2: The statement that incidence of hippocampal metastases was low was added.
Change in the text: see Page 2, line 33-36.

Comment 3: Please include a Statement about neurocognitive decline in More Details, please also include a state of the Art reference to Medication for prevention of neurocognitive decline.
Reply 3: A statement about neurocognitive decline, including the efficacy of memantine was added.
Change in the text: see Page 2, line 21-28.

Reviewer B

Comment 1: Please use "might" instead of "will", since we don't yet know the results and what their impact might be.
Reply 1: "will" was changed into "might".
Change in the text: see Page 4, line 61.

Reviewer C

Comment 1: Cost-effectiveness of MRI and PCI (or HA-PCI)
Recently, several studies evaluated the cost-effectiveness of MRI surveillance and PCI (or HA-PCI).

In a situation where the survival benefit of PCI is not clear, cost-effectiveness will be an important factor when determining the most proper strategy in clinical practice. Please add some comments from authors related to following references.

References

 Cost-effectiveness of prophylactic cranial irradiation with hippocampal avoidance in limited stage small cell lung cancer (Radiother Oncol. 2017 Mar;122(3):411-415. doi: 10.1016/j.radonc.2017.01.005. Epub 2017 Jan 18.)

 Cost-Effectiveness of Prophylactic Cranial Irradiation Versus MRI Surveillance for Extensive-Stage Small Cell Lung Cancer (Int J Radiat Oncol Biol Phys. 2021 May 11;S0360-3016(21)00477-6. doi: 10.1016/j.ijrobp.2021.04.049. Online ahead of print.)

Reply 1: We cited the latter reference and added a comment on that.

Change in the text: see Page 3, line 47-48.

Comment 2: The need for brain MRI

For baseline images or follow-up images? In this manuscript, there are parts of confusion about which MRI is meant. However, I think it is important to mention the two separately.

When brain MRI was performed before PCI, to what extent is the rate of newly developed brain metastases reported in existing studies? In addition to the detection of those unexpected new brain metastases, baseline MRI is essential for hippocampus delineation in HA-PCI.

Furthermore, when periodic MRI examination is performed during follow-up, to what extent is the rate of newly developed brain metastases reported in existing studies? The frequency might vary greatly depending on the risk factors the patients have. A different approach may be required for each patient. It would be better if you add these contents to your manuscript.

Reply 2: In our manuscript, we used "MRI" in the latter meaning. We searched data regarding how frequently brain metastases is detected on MRI before PCI and distinct patient characteristics associated with brain metastases tendency. However, we could not find any. Thank you for your insightful comment.

Change in the text: none.

Comment 3: Integration of immunotherapy agents such as atezolizumab

FDA approved the use of atezolizumab in extensive stage SCLC in 2019. Integration of immunotherapy agents such as atezolizumab showed reduced incidence of brain metastases by more than 50% in several studies. It might thereby reduce the benefit of PCI. This fact will influence the physician's choice of whether to perform PCI.

Reply 3: We could not find any efficacy data of atezolizumab for brain metastases in SCLC. We will see until such data are obtained. Thank you for your educational comment.

Change in the text: none.

Comment 4: Memantine

In NCT01780675 trial, memantine was not part of the treatment, in contrast to the CC001 trial. It might had underestimated or overestimated the beneficial effect of hippocampal-avoidance than previous studies. This point must be taken into account when designing a study “HA-PCI versus no PCI only with MRI surveliance” and interpreting the results. Please provide some opinion of yours.

Reply 4: As the reviewer pointed out, memantine was not part of the treatment in the NCT01780675 trial. In my opinion, CC001 trial and NCT01780675 trial are different in many points, such as primary site (lung SCLC vs many), and RT timing (PCI vs WBRT). Therefore, we did not argue intensively in our manuscript. Thank you for your excellent comment.

Change in the text: see Page 2, line 21-28.

Comment 5: PCI in limited-stage SCLC in the MRI era

In this manuscript, authors said than the significance of PCI for limited stage SCLC in the MRI era in still uncertain. Although a well-designed randomized study is necessary, an interesting attempt has been recently made by the MDACC group. They analyzed limited-stage SCLC patients with or without PCI treated in the MRI era (all underwent at least baseline MRI, with restaging brain MRI and/or computed tomography). Please add relevant content to the appropriate location in the manuscript.

References

□ The Role of Prophylactic Cranial Irradiation in Limited Stage Small Cell Lung Cancer in the MRI Era (Int J Radiat Oncol Biol Phys. ABSTRACT ONLY| VOLUME 108, ISSUE 2, SUPPLEMENT , E23, OCTOBER 01, 2020)

 Rates of Overall Survival and Intracranial Control in the Magnetic Resonance Imaging Era for Patients With Limited-Stage Small Cell Lung Cancer With and Without Prophylactic Cranial Irradiation (JAMA Netw Open. 2020;3(4):e201929. doi:10.1001/jamanetworkopen.2020.1929)

Reply 5: We cited the latter reference and added a comment on that. We appreciate reviewer's appropriate suggestion.

Change in the text: see Page 3-4, line 56-59.

Comment 6: PCI in Extensive-stage SCLC in the MRI era

After Japanese trial was published, some retrospective studies which analyzed only patients who treated during MRI era or whom MRI was performed before PCI or as surveillance. I think those studies can provide important information, although there may be limitations in interpreting the conclusion. Please add some results of those studies in your manuscript.

Reply 6: We cited two references and added a comment on those. We appreciate reviewer's appropriate suggestion.

Change in the text: see Page 3, line 45-46.

Reviewer D

General comments:

This letter is an important contribution and I recommend that it be accepted for publication.

Specific comments:

None.

Reviewer E

Well written letter to the editor. The authors have made their point.