Author's response to reviews

Title: Adaptation of Magnetic Resonance Imaging and Stereotactic Irradiation for Management of Brain Metastasis Attenuated Benefits of Prophylactic Cranial Irradiation in Patients with Limited-Stage Small Cell Lung Cancer

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Author's response to reviews: see over
Dear Associate Editor,
Dr. Aaron H. Wolfson,
Dr. Paul Rava,

Re: BMC cancer – Decision on Manuscript ID 3088891001428205

Dear Associate Editor,
Dr. Aaron H. Wolfson,
Dr. Paul Rava,

Thank you very much for your comment with regard to our manuscript together with the constructive advice. These comments have been very helpful in allowing us to improve our manuscript. We have attempted to address the questions you raised.

Our-point-by-point responses are below. And we provide a highlight copy of the manuscript which shows the alterations that have been made with underline.

We believe that the manuscript has been improved satisfactorily and hope that it will be accepted for publication in BMC Cancer.

Yours sincerely,

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Dear Dr. Aaron H. Wolfson,

Major compulsory revisions.

1. **Lack in references for the difficulty of treating brain metastasis.**

   We are sorry for not citing adequate references and appreciate your precise pointing out. What we wanted to say was that brain metastasis needed radiotherapy to be controlled and whole brain radiotherapy is not adaptable repeatedly, however we agreed that our description and reference were not sufficient and adequate including Chang’s report.

   In this revision, we deleted the sentences and the citations (page 5, line 22-24, page 6, line 1-2, 5-10) and replaced to the new sentences at page 6, line 89-95 with new citations including Harris’s report (Int J Radiat Oncol Biol Phys, 2012).

   We also changed the order of the sentences and added some description, which are underlined in the revised manuscript. We believe it makes our hypothesis more clear and easy to understand.

2. **Citation of the paper by Chang, et al. to say the possibility of harmfulness with whole brain radiotherapy in patients with SCLC is not adequate.**

   As described above, we agreed that Chang’s paper is not an adequate reference and does not support our hypothesis.

   However, Harris, et al. reported that BM newly developed after PCI or WBRT did not progress locally at 57% in one year and 34% in two year, respectively. In addition, 42% in one year and 25% in two year were also free from distant BM development, too.

   Considering the poor prognostic background of included patients and the high ratio of (76%) of multiple BM in the study, we think the reported MST, 5.9 months, is good enough to consider a possibility that SRI in patients with SCLC could improve survival.

   We added the description at page 6, line 89-95, as mentioned above.

3. **There is no reasonable hypothesis for using SRI in the current population versus PCI.**

   As described above, we agreed that Chang’s paper is not an adequate reference and does not support our hypothesis.

   However, Harris, et al. reported that BM newly developed after PCI or WBRT did not progress locally at 57% in one year and 34% in two year, respectively. In addition, 42% in one year and 25% in two year were also free from distant BM development, too.

   Considering the poor prognostic background of included patients and the high ratio of (76%) of multiple BM in the study, we think the reported MST, 5.9 months, is good enough to consider a possibility that SRI in patients with SCLC could improve survival.

   We added the description at page 6, line 89-95, as mentioned above.

4. **The sample size is too small to make reasonable statistical comparison to the 95 non-PCI patients cohort for using MRI to evaluate the two patient cohorts regarding outcome.**

   It is true that the number of cases in our study is small and we understand your concerns. According to the historical data, PCI reduced a risk of death just 16% (HR 0.84) (Auperin, et al. N Engl J Med, 1999) and we agreed that our study does not have sufficient number of cases for the survival time, and we emphasized the deficiency of power, at page 11, line 206, and line 213-216.
However, we would be very grateful if you could notice that previously reported risk
reduction on brain metastasis was 54% (HR 0.46) (Auperin, et al. N Engl J Med, 1999)
and, because of the high effectiveness, current study’s sample size is supposed to have
power of 70-75% to detect 5% difference (Lakatos, et al. Biometrics, 1988. Lakatos, et al,
Statistics in Medicine, 2002), which is not very strong, but we think it is acceptable.

**Minor Essential revisions:**

1. **Page 8, lines 5-9: Should consider referencing all listed statistical tests.**
   
   We appreciate your advice, and added a description in the method session, at page 8,
   line 139-141.

2. **Page 8, line 17: What is meant by “CR ratio”?**

3-5. **Figure 1-3: Should give legend on Figure for defining “PCI”, “M”, and “D”.**

   Thank you for pointing our fault.

   We replaced the “CR ratio” to “ratio of CR”, and added the definition of PCI on each
   figure legends.
   “M” and “D” in figures were replaced by “months” and “days”, and explanation for M
   and D were added to the legends, respectively.
Dear Dr. Paul Rava,

Minor revisions.

1. The Background is unclear. The small numbers of enrolled patients should be addressed.

Thank you for the useful advises. As suggested, we rewrote background session and emphasized the clinical importance of cranial MRI. The revised sentences are underlined, which are mostly at Page 5, line 68-74, and page 5, line 81-page 6, line 100.

We agreed with you that we should emphasize the limitation of number of cases, and added some descriptions in the discussion session, at page 11, line 206, and 213-216.

Major compulsory revisions.

1. Statistically significant difference of staging needs to be emphasized in the results and the discussion session.

We agreed that the difference of staging affected the results strongly, and, as indicated, we added some explanations about the difference of the clinical stage and possible advantageous for non-PCI group in both of the results and discussion session (page 8, line 146-148, page 10, line 192-194).

2. The discussion is lacking in patients who received MRI and did not receive PCI were at lower risk of brain metastasis than historical records.

The 2-year-occurrence rate of brain metastasis in patients who received MRI in non-PCI group was 38.4% in a present study, which is lower than that previously reported, 50-60%. All reported BM incidences are shown below (ref.#1-4, and #6-20).

In the original manuscript, we first described that previous studies showed 40-60% of BM incidence because Arriagata, et al. reported around 40%. However, the incidence was calculated with only BM which isolated as first site of failure. Because our study include all BM, we think it should be 50%-60% based on previous studies.

We apologize for the showing of wrong frequency, and changed the description about the BM incidence to 50-60%. The sentences are at pate 5, line 60, 79, and added some descriptions about the comparison between the present and previous results are at page 10, line 191-192.

List of BM incidence in previous studies (#1-4, #6-20).

#1. Auperin, et al. review of papers below. (around 60% as merged, all BM)  
3. Number of patients who developed brain metastasis is too small for a good comparison, and the reason why the patients in PCI group received PCI is unclear.

Thank you for your appropriate advices.

We totally agreed with you that the number of cases were small. However, according to the previously reported great benefit (HR 0.46) (Auperin, et al. N Engl J Med, 1999) on the prevention of brain metastasis by PCI, our current number of cases are supposed to have power of 70-75% to detect 5% difference for that (Lakatos, et al. Biometrics, 1988. Lakatos, et al. Statistics in Medicine, 2002). According to these, we hopefully think it is acceptable.

About the reason for the performing PCI, because this is a retrospective study, all depended on the decisions by the physicians, and there is no clear criteria. We realized that it is one of major limitations, and described at page 11, line 216-217.

4. Citation of Wegener’s paper is not correct.

We appreciate your proper pointing our wrong citing. We deleted the sentences citing Wegener’s paper from background session and replaced to new sentences citing new references (S. Harris, et al. Int J Radiat Oncol Biol Phys, 2012, and others), at page 6, line 89-95.
We cited Wegner’s paper in discussion session for the discussion about the effectiveness of SRI in patients with SCLC, at page 11, line 202-203.

5. The Chang’s paper is not adequate to tell whole brain radiotherapy may be harmful for patients who received SRI for brain metastasis.

We appreciate you for indicating us appropriately the defects of our citation. We totally agreed with you and apologize deeply for a wrong citation and description. We deleted the sentences and replaced the citation to new papers (S. Harris, et al. Int J Radiat Oncol Biol Phys, 2012, and others).

The replaced sentences are at page 6, line 89-95 in background session, and from page 10, line 198 to page 11, line 206 in the discussion session.

We hope these changes help readers understand our study more easily and clearly.

6. Our current study may be stronger study if it were focus on the incidence of brain metastasis in a patient population that did not receive PCI, and discuss the merits of re-evaluating this question in the era of improved brain imaging.

Thank you very much for your constructive advices and informing us a valuable report by Linlin Gong, et al. We totally agreed with you that we had better focus the era of improved brain imaging.

However, only 60% in non-PCI group received cranial MRI before PCI in current study and we focused on to determine whether PCI is less beneficial than that previously reported under the adaptation of cranial MRI and SRI or not.

According to the promising results of a present study, we determined to proceed for further investigation and are currently proceeding with a prospective, observational study focusing on the impact of cranial MRI. We are hopefully expecting that our next study can provide more data about the merit of re-evaluation with improved brain imaging.

We added a description about the proceeding observational study at the end of conclusion session, at page 12, line 229.