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
Dr. Adilia Hormigo,
Associate Editor of BMC cancer,

Re: BMC cancer – Decision on Manuscript ID 3088891001428205

Dear Dr. Hormigo,

Thank you very much for your email dated April 28, 2015 with regard to our manuscript together with the comments from the reviewer. These comments have been very helpful in allowing us to improve our manuscript again. We have attempted to address the questions raised the referees. Our-point-by-point responses to the reviewer’s comments are attached and we provide a highlight copy of the manuscript that 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,

Minor revisions.

1. Referencing the Kaplan-Meier method, student’s t-test, and the Cox proportional hazards regression model in the methods section.

As suggested, we have cited new references (#26, 27) for the statistical methods.

And, because we have deleted the description in Results (L178-L182) about further analysis in patients with brain metastasis during observation period to clarify the points, we deleted a description about the cox proportional hazards regression model in the method section, too.

2. Word “enrollment” is misspelled.

We have corrected some spelling errors including this. And another native speaker of English improved our manuscript.
Dear Dr. Paul Rava,

1. **Improve the language throughout.**

   We have corrected any spelling and grammatical errors. And another native speaker of English improved our manuscript. We have modified the Introduction and Discussion to clarify the points.

2. **There is no enough evidence to conclude, “no clear improvement in survival or BM incidence was observed following PCI”.

   As the reviewer kindly suggested, we should not overestimate the results in our retrospective study. We have modified the descriptions in Abstract and Discussion. And we have deleted the description in Results (L178-L182) about further analysis in patients with brain metastasis during observation period to clarify the points.

   As described in the limitation in Discussion, it was a small study. We agreed with that number of cases in current study is not enough to modify or change the current guidelines. However, our study is supposed to have power of around 70% to detect 5% significance level even with the consideration for the imbalanced number in the two groups, as mentioned in the response to previous review. Although current standard treatment is to do PCI in patients with good responses to initial treatment, strategy can be re-evaluated according to advances in cancer therapy. At present, assessment with MRI before PCI becomes common to detect brain metastasis in some institutes, which is different from the situation that previous clinical trials were done. We believe our study can offer the opportunity to reconsider the benefit of PCI in the current situation that the management with MRI and SRI are available.

3. **The number of patients was imbalanced between the PCI and the non-PCI groups. The patients with an MRI prior to treatment should be compared.**

   It is true that cases in the two groups were imbalanced. The ratio of clinical stage III patients was significantly higher in the PCI group, which would be advantageous for the non-PCI group. On the other hand, other factors, including younger age and the higher ratio of CR, were advantageous for the PCI group. Because the benefit in PCI group was similar to those in non-PCI group in the present study (in contrast with previous studies reporting that PCI group can receive benefit from PCI), higher ratio of stage III patients in the PCI group might to cause reduction of the benefit of PCI. So we analyzed only patients with stage III disease and showed similar occurrence of brain metastasis and survival (Fig. 2).

   On the other hand, the age was young and the ratio of CR and MRI confirmed absence of brain metastasis were high in the PCI group. These features are better characteristics that favor the beneficial outcomes. We would be most grateful if the reviewer could take a notice that some differences were advantageous for the PCI group.

   In the present study, 57 patients (60%) in the non-PCI group and 28 patients (96%) in the PCI groups received an MRI prior to PCI. Assessment with MRI confirmed patients were free from brain metastasis, and this difference was advantageous for PCI group. However, again, there was no difference in PCI benefit in two groups. We have
added the description about the analysis of subgroups that received MRI immediately before PCI. (L142-144)