Author's response to reviews

Title: Is stereotactic radiosurgery a rational treatment option for brain metastases from small cell lung cancer? A retrospective analysis of 70 consecutive patients

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Title: Is stereotactic radiosurgery a rational treatment option for brain metastases from small cell lung cancer? A retrospective analysis of 70 consecutive patients

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We are most grateful to you and the reviewers for the helpful comments regarding the original version of our manuscript. According to the constructive comments provided, we have now appropriately addressed all concerns. Herein, we respond to each of the issues raised by the reviewers, as follows:

Reviewer #1:

In response to reviewer #1 comment 1a [It would be very helpful to include an analysis of the risk factors associated with distant brain failure after SRS, focusing on those patients who received SRS only for newly diagnosed small cell lung ca brain metastases. It is necessary to determine whether the number of brain metastases correlates with the risk of distant brain failure.] and reviewer #2 recommendation [remote recurrence should be analyzed from the patients with follow up imaging data.”], we reanalyzed the dataset limited to 60 patients with MR imaging follow-up. Although we observed a higher probability of distant recurrence in patients with multiple BM after upfront SRS, the difference did not reach statistical significance (Gray’s test, $p = 0.085$), probably due to the lack of statistical power (n = only 40, upfront setting).

![Graph showing cumulative incidence of distant recurrence](image)

We also performed a multivariate analysis to examine the probability of distant recurrence, which unfortunately revealed no significant clinical factors (Fine-Gray proportional hazard test).

### Analysis of factors predicting distant recurrence after SRS (Fine-Gray proportional hazards model)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>P value</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young ($\leq 65$ years)</td>
<td>0.25</td>
<td>0.584 (0.232-1.47)</td>
</tr>
<tr>
<td>High KPS ($\geq 90$)</td>
<td>0.85</td>
<td>1.10 (0.415-2.90)</td>
</tr>
<tr>
<td>Controlled extra-CNS disease</td>
<td>0.57</td>
<td>1.54 (0.351-2.08)</td>
</tr>
<tr>
<td>Post-SRS chemotherapy</td>
<td>0.74</td>
<td>1.29 (0.289-6.74)</td>
</tr>
<tr>
<td>Single BM</td>
<td>0.22</td>
<td>0.414 (0.103-1.67)</td>
</tr>
</tbody>
</table>

SRS stereotactic radiosurgery, KPS Karnofsky performance scale, CNS central nervous system, BM brain metastases
We appreciate that, from the clinical viewpoint, this observation is of critical importance for devising an appropriate treatment strategy and follow-up, though the data are as yet preliminary. We are reluctant to show these apparent preliminary results, as a false message might be given to readers. However, we hope to address these important issues in future investigations.

In response to reviewer #1 comment 1b [Please include the range for the median follow-up (Line 155)], we added the range for the median follow-up as follows;
“The median follow-up time after SRS was 7.8 months (range: 0.6-56 months).” (Line 158)

In response to reviewer #1 comment 1c [How did the authors determine whether it was tumor progression or radiation necrosis? (Line 182)], we apologize for the inappropriate description. In this patient, we observed only progressive enlargement of the brainstem enhancement and edema on follow-up MR imaging coupled with neurological deterioration, without autopsy. It is theoretically impossible to determine whether it was true recurrence or radiation necrosis or both, though we a priori assumed it to be recurrence. Accordingly, “local tumor recurrence” was modified to “local control failure” (Line 186).

Reviewer #2:

In response to reviewer #1 comment 1a [Radiosurgical indication needs to be clarified. The fact that cancer board of referring regional hospitals had determined the appropriateness of SRS suggests there might be serious selection bias. What are the authors universal selection criteria if they would not treat all the referred patients automatically? Particularly, indication in upfront setting needs to be described in detail so that it explain how recommendation of radiosurgery instead of WBRT could be justified.], we already described in detail our radiosurgical indications in the methods section as follows (still insufficient?);
“In the upfront setting, patients with up to ten BM principally received SRS. When abnormal enhancement of cranial nerves, the ventricular ependymal layer and/or the cortical surface or more than 10 BM were documented by high resolution magnetic resonance (MR) imaging at the time of initial SRS, WBRT was recommended. In the salvage setting, the treatment protocol in the author’s institution has no set limit on the number of BM. Providing that WBRT had either already been performed or refused by the patient, SRS was applied for multiple BM, even in cases with more than 10 lesions, when the patient’s systemic condition was such that SRS intervention would be tolerable and fully informed consent for treatment had been obtained.” (Line 90-98)

In response to reviewer #1 comment 1b [Criteria of ‘large tumors’ which were treated with 2-session radiosurgery should be described.], we added a detailed description for “large tumors” in the methods section as follows;
“Surgical resection was, in principle, indicated for large tumors (≥10mL) with a mass effect unresponsive to corticosteroid therapy. If surgery did not seem feasible due to a poor prognosis or advanced systemic disease, 2-session SRS was indicated for carefully selected large tumors (≥10mL).” (Line 98-100)

In response to reviewer #1 comment 1c [Selection criteria for salvage treatment modality should be clarified too. The same selection criteria as in the first radiosurgery or WBRT?], we added the following sentence in the methods section;
“When miliary metastases (numerous tiny enhanced lesions) and/or leptomeningeal carcinomatosis was newly documented, WBRT was then considered unless it had been used previously.” (Line 117-119)

In response to reviewer #1 comment 1d [Local control failure and remote recurrence should be analyzed from the patients with follow up imaging data. For example, 33 patients with remote recurrence are 55% of 60 patients with follow up imaging.], we reanalyzed the dataset limited to 60 patients with MR imaging
follow-up. The 6- and 12-month actuarial rates of remote BM relapse were estimated to be 25% and 47%, respectively (higher than the previous version). The abstract, results, Fig. 2A and figure legends were modified accordingly, as follows;

“Six- and 12-month rates of remote BM relapse were 25% and 47%, respectively.” (Abstract, Lines 40-41)

“Remote metachronous BM were observed in 33 patients (55%). The 6-month and 1-year remote BM recurrence rates (per patient) after SRS were 25% and 47%, respectively (Fig. 2A).” (Results, Lines 177-178)

“The 6- and 12-month distant intracranial recurrence rates were 25% and 47%, respectively.” (Figure legends, Lines 435-436)

In response to reviewer #1 comment 1e [Table 5. “Low marginal dose (> 20Gy)” should be “Low marginal dose (< 20Gy)”], we apologize for this careless error. “Low marginal dose (> 20Gy)” in Table 5 was corrected to “Low marginal dose (< 20Gy)”.

This revised version of the manuscript was thoroughly proofread by a professional medical editor who is a native speaker of English.

We are doing our best to meet the high standard of BMC Cancer, and we believe that quality of the manuscript has been improved as a consequence of the revision. However, we would be happy to revise the manuscript again (if necessary). Thank you very much for your time and efforts in editing and reviewing our manuscript.

Sincerely,

Shoji Yomo, M.D., Ph.D.