Reviewer’s report

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

Version: 2
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Reviewer: Paul Rava

Reviewer’s report:

The premise of this manuscript is whether PCI provides a benefit for patients with LS-SCLC. To shed light on this the authors evaluated patients with LS-SCLC treated in Japan who obtained a complete or good response to definitive thoracic treatment and then received, or did not receive, PCI. A total of 124 patients met inclusion criteria and were analyzed (29 in the PCI group and 95 in the no PCI group). Upon analysis each group did vary with respect to age, response to thoracic treatment, performance status and clinical stage. 96.5% of the PCI group was confirmed to not have BM prior to radiation while only 60% of those in the no PCI group. There was no difference in OS between the two groups. With respect to CNS disease there was a difference in the incidence of new brain metastases. These were salvaged with either stereotactic radiation or WBRT. The authors discuss the relevance of their findings focusing the discussion on previous PCI studies, on which current standards are based, which were not done in the era of MRI and most did not require effective brain imaging prior to PCI. Their rates of new metastases in the observation period are low, especially in stage III patients (~10%), suggesting that the benefit historically described in the literature may not be representative of the current patient population. In all the manuscript is thought-provoking and of interest to the oncology community as there are neurocognitive effects associated with whole brain radiation.

However, there are some major concerns.

Minor revisions.

1. The background is unclear and should be re-written. The study appears to address the impact of MRI in defining current patient risk of BMs in LS-SCLC and less that of SRI or PCI on impacting outcomes. Specifically, the small numbers (especially in the PCI group) do not allow a comparison of survival. This should be addressed.

Major compulsory revisions.

1. There is a statistically significant difference between staging of the two groups which overwhelmingly favors the outcomes of survival and development of brain metastases for those in the non-PCI group. This point needs emphasis in the manuscript in both the results section and the discussion.

2. The discussion is lacking in that it does not emphasize the major result in that
patients who receive an MRI following definitive treatment and who do not receive PCI are at lower risk of brain metastases than historically described.

3. While there is some evidence from the patients described here that SRI at the time of BM might be an acceptable alternative, the number of events is small and the number of patients in the PCI group is too small for a good comparison. Also as to why these patients received PCI is unclear and may be biasing the results.

4. The Wegener et al. citation does not support that BM from SCLC is less rapid than previously thought. It shows that a highly selected group of patients who develop brain metastases following PCI can be salvaged effectively with SRI and that for these patients such salvage may be beneficial.

5. The Chang et al. study is the only study to show a survival advantage with SRI and given that the SRI+WBRT group had overwhelmingly better intracranial control than the SRI group only, it is unclear why there was such a dramatic difference in survival, and that this favors the SRI group only. Also, it was stopped early resulting in an imbalance between the arms and few number of patients for a real comparison and conclusion.

6. This may be a stronger study if it were to focus on the incidence of BMs 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. The risk of BMs is multifactorial and omitting PCI given the previous level I evidence in all-comers is somewhat premature based on the low numbers of patients and events described in the current text. A similar article was recently reviewed and published in the International Journal of Radiation Oncology Biology, Physics by Linlin Gong et al. (IJROBP 85(1):196).

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests