Author’s response to reviews

Title: Survival and clinical outcomes of patients with melanoma brain metastasis in the era of checkpoint inhibitors and targeted therapies

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Version: 1 Date: 02 Mar 2018

Author’s response to reviews:

Dear Dr. Rao,

We thank you and the reviewers for the thorough review and thoughtful comments on our manuscript. Attached please find a revised manuscript, along with a point-by-point response to the reviewers’ comments. We have revised the manuscript significantly to address their comments. The edited sentences and paragraphs are highlighted in yellow.
The reviewers commented on the lack of certain details on patient characteristics (such as Karnofsky Performance Status or intracranial disease control) in the cohort. Although their comments are appropriate in the context of a clinical trial examining a given therapeutic modality, we would like to emphasize that the primary aim of our study was to assess the overall survival associated with this advanced stage of melanoma in a real-world situation, in the era of novel checkpoint inhibitors and targeted therapies. As our study was a retrospective study, we were unable to capture some of the types of data requested by the reviewers. Nevertheless, our data showed a longer survival duration of metastatic melanoma involving the brain than other historical studies, and identified novel factors associated with altered survival, including factors that were independently predictive of survival on multivariate analysis. The median overall survival of those with melanoma brain metastasis is now longer than 1 year, and nearly 3 years for those who were treated with anti-PD-1 antibody. As a result, we believe that our findings provide important information for treating oncologists and patients alike in order to be aware of the revised natural history of metastatic melanoma with brain metastasis as a prelude to making appropriate management decisions.

We hope that the manuscript can be acceptable for publication in BMC Cancer.

Thank you for your consideration of the revised manuscript.

Sincerely,

Kevin B. Kim, M.D.

Reviewer #1

We thank the reviewer for the constructive comments provided.

The article examines a series of <80 patients from a single medical center with neurosurgical capabilities (surgery, SRS), radiation oncology, and oncology with advanced treatment algorithms. The question asked in this paper is relevant and important especially in counseling
patients and family in regards to prognosis. However, the limited data and confounding variables make the conclusions difficult to accept.

- What else is different with the historical control when comparing OS? Was whole brain being utilized more that surgery/SRS? Was there ever a change in the treatment algorithm with the utilization of surgery and/or SRS in treating melanoma brain metastases? Clarification in the discussion would be useful.

- Davies and colleagues showed that there was no significant difference in the median overall survival duration between melanoma patients with brain metastasis diagnosed prior to 1996 and those diagnosed between 1996 and 2004 [Ref: Davies et al. #4]. Although stereotactic radiosurgery was likely used more frequently in the latter time period, there was no significant overall survival improvement noted in the overall population of patients with brain metastasis. In their study, the median overall survival duration in patients who were initially treated with a stereotactic radiosurgery was 7.69 months, whereas the median survival was 15.4 months post stereotactic radiosurgery in our study. Therefore, we believe that the change in the radiotherapy treatment algorithm for brain metastasis has had a minimal impact in overall survival in this patient population. As a result, the improvements noted in our cohort are likely to due to the availability and activity of the novel systemic therapies, including checkpoint inhibitors and targeted therapy drugs. This was added in the discussion section (page 11, line 7-19) as recommended by the reviewer.

- How can you clearly show that the overall survival change conferred with the studied treatment is due to effects on brain metastases and not other disease in the body? Did all patients die from neurological ailments relatable to brain metastases? The Sampson paper mentioned in the discussion examined 702 patient from a large center. If the point being made is that melanoma patients with brain metastases die from intracranial disease, it would be helpful to mention the rate in your cohort or at the very least expound on the Sampson data in the introduction and justify why the study was undertaken.

- Brain metastasis is the likely a cause of death in a vast majority of melanoma patients with brain metastasis. Sampson et al. (ref #16) showed that among 702 patients with melanoma brain metastasis, the median survival duration was 113.2 days (less than 4 months), and brain metastases contributed to the death of 94.5% of the patients. Although our database did not include detailed information regarding neurological symptoms at the time of death, we believe
that most of our patients died due to progressing CNS disease. This was added in the discussion section as recommended by the reviewer (the 1st paragraph). In addition, our results are complemented by recent clinical trials showing the activity of these newer therapies specifically in controlling CNS disease (reference #19, 20, 21, and discussed on page 13, line 1-4).

• The fact that many patients received systemic therapy prior to the diagnosis of brain metastasis further convolutes the analysis and the conclusion.

– We agree that the prior systemic therapies can potentially complicate the analysis of outcome of patients with brain metastasis. However, there is no way to control for that, and the goal of our study was to assess the survival of patients with melanoma brain metastasis following the initial diagnosis of brain metastasis. However, during the time frame of our study, checkpoint inhibitors and targeted therapies were not approved for use in the adjuvant setting. In addition, our analysis of treatment with various drugs assessed their use specifically in the setting of brain metastasis. In fact, in the case of anti-PD-1 antibody therapy, only 1 patient had received anti-PD-1 antibody prior to diagnosis of brain metastasis, and the prolonged overall survival of with anti-PD-1 antibody therapy was demonstrated by both univariate and multivariate analysis. Therefore, the likelihood of this acting as a confounding factor is quite low.

• The multivariate analysis results seem affected by low N as certain factors such as adrenal involvement or cerebellar involvement were significantly and independently predictive of survival.

– We agree that the number of patients in certain categories is low, especially for those with adrenal gland metastasis. However, these factors retained their significance in multivariate analysis due to their strong impact on survival (a hazard ratio of 9.94, p=0.027). Nevertheless, this limitation was described in the discussion section (the 6th paragraph), and we included a statement that this observation should be confirmed in large cohorts.

Minor points:

• Page 4 “Still most patients are being told…” is not a very objective or proper statement for a scientific journal and should be restated.
– The sentence was changed to “However, these studies do not address the survival outcomes of patients who are not candidates for systemic therapies or clinical trials. Therefore, there is a lack of current survival data in patients with melanoma brain metastasis in a real world situation in the modern era”

In addition to the changes in the revised manuscript as indicated above, we updated the reference (#21) as they were published since our original manuscript was submitted.

Reviewer #2

We thank the reviewer for the gracious comments regarding the manuscript.

The authors provide a detailed retrospective review of survival data from their institution for individuals with metastatic melanoma harboring CNS metastases. Their hypothesis poses that survival has been improved in the era of targeted therapies including BRAF/MEK inhibitors as well as checkpoint inhibitors, and relative to historical controls of individuals with brain metastases from melanoma, the data presented supports increased survival in the age of checkpoint inhibitors. The authors retrospectively reviewed their institutional database from 2011 to 2015 and identified 79 patients. Survival from time of diagnosis with a brain metastasis was approximately 12 months with improved survival associated with craniotomy, SRS, and treatment with a PD-1 inhibitor.

While the authors should be commended on their analysis there are several shortcomings.

• The strength of their conclusions would be increased if there was a comparison to survival of individuals at their institution prior to the initiation of targeted therapy of checkpoint inhibitor. Their analysis includes only patients treated after the initiation of these therapies with comparison to historical controls reported in the literature.

– We agree that the comparison with our historical data would make our manuscript more meaningful. Unfortunately, our database system prior to 2010 was not comprehensive enough for us to investigate the survival outcome of all patients with brain metastasis. However, there is no
reason to believe that survival outcomes of our patients prior to 2011 would be much different from what are available from the literature at that time. The treatment modalities prior to 2011 included surgery, radiation therapy, chemotherapy and/or cytokine therapy in our institution, similar to most other centers, and it is difficult to imagine that clinical outcome in our patients prior to 2011 would be better than other institutions.

- Additionally, while they do report on the extracranial disease status, there is no report of other factors such as KPS or RPA that have a known effect on survival and are more standardized metrics reported in the neuro-oncology literature.

– We agree with the reviewer regarding the potentially useful information that can be provided by such data. As our analysis is a retrospective study (and not a prospective clinical trial), we were unable to capture such detailed, but relevant data. Some of the patients were diagnosed with brain metastasis at another institution and later transferred their care to our center, and the patients’ performance status and neurological assessment at the time of the brain metastasis were not available to us. The large series of patients with brain metastasis, such as Sampson et al. (ref #16) and Davies et al. (ref #4) also did not describe the KPS and RPA of patients when they analyzed their clinical outcome.

- Furthermore, it would have been useful if the authors reported on local and distant intracranial disease control in these individual treated with targeted and checkpoint inhibitor therapy. While overall survival is ultimately an important metric of these therapies effectiveness, it would have been useful to include a discussion of CNS disease control by these agents as well.

– The main objective of our study was to assess the overall survival outcome in the era of the novel immunotherapy and targeted therapy. Although the pattern of intracranial clinical responses and disease progression on these drugs would have been useful, many patients received a combination of treatments (such as stereotactic radiosurgery immediately followed by immunotherapy and/or BRAF inhibitor), and this made the detailed analysis on the evaluation of clinical response/progression difficult. In addition, our results are complemented by recent clinical trials showing the activity of these newer therapies specifically in controlling CNS disease (reference #19, 20, 21, and discussed on page 13, line 1-4). However, we accept that this is a limitation of retrospective studies, such as our manuscript. This limitation has been described in the discussion section (page 13, line 4-8).
• I suspect that the patient numbers were too small to support meaningful statistically analysis of this.

– Yes, we agree. Our results strongly suggests the improvement of survival outcome in this patient population likely due to the availability of the novel targeted drugs and checkpoint inhibitors; however, the numbers were too small for adequate statistical analysis. Rather than proving the survival outcome improvement with the novel drugs, our study focused on the description of overall survival outcome in melanoma patients with brain metastasis in a real life community practice setting. The specific support from this comes from recently conducted prospective trials of these agents (reference #19, 20, 21, and discussed on page 13, line 1-4). However, our study is different because it is analyzing the natural history (i.e., overall survival) of melanoma brain metastasis, whereas a clinical trial typically reports on survival parameters from the onset of a given treatment.

• Finally, the authors conclude the anti-PD1 treatment trended towards significance for improved survival but it was not clear whether these individuals had similar baseline demographics to those that did not receive this treatment with respect to number of metastases, functional status, or associated treatment (SRS and craniotomy).

– As described above, we were not able to assess some detailed patient characteristics in our study. The multivariate analysis does include the major factors that have been shown to alter survival in the setting of melanoma brain metastasis. In addition, as mentioned previously, our discussion includes the recent prospective studies which evaluated the clinical outcome of melanoma patients with brain metastasis who were treated with dabrafenib/trametinib combination or nivolumab/ipilimumab combination (reference #19, 20, 21, and discussed on page 13, line 1-4). These studies have clearly demonstrated a meaningful clinical benefit with these novel drugs, which was strongly suggested by our survival analysis.

• I agree with the authors that the paradigm shift in the treatment of metastatic melanoma requires reevaluation of survival and even the effectiveness of these agents in controlling CNS disease, but the conclusions and analysis could be strengthened by the above.

- In addition to the changes in the revised manuscript as indicated above, we updated the reference (#21) as they were published since our original manuscript was submitted.