

São Paulo, August 23, 2023

Letter to Editorial Board of the World Journal of Clinical Oncology

Dear Editors,

Thank you for completing the examination of our manuscript “Evaluation of Toxicity and Survival of Patients with Multiple Brain Metastases Treated with Isolated Radiosurgery”.

We have prepared a revised version addressing all the issues the reviewers raised. We have carefully gone through the manuscript to make the appropriate changes in the text (highlighted in Yellow). Also, all answers for the reviewers are answered below, point-by-point. We hope that our article will be suitable for your prestigious journal.

Thank you in advance for your time and consideration.

Sincerely,

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Reviewer 1

Scientific Quality: Grade E (Do not publish)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: *Dear Authors, Congratulations with the article*

"Evaluation of Toxicity and Survival of Patients with Multiple Brain Metastases

Treated with Isolated Radiosurgery". However I do have some major concerns:

Point 1 - Methods - patient selection: Please be more elaborate about patient

selection criteria, were only 55 patients treated during August 2017 ending February

2020? probably not, did you exclude patients from your study? why? If necessary,

make a flow chart regarding patient selection. This to show any patient selection bias

Answer: Thank you for your review and comments, they improved the quality of our manuscript, and we appreciate it. Considering the study design of this retrospective cohort, and the use of radiosurgery for 4 or more brain metastases, 55 patients were included in a period of 30 months of our practice. This project raised the question about the toxicity of radiosurgery for 4 or more brain lesions since the use of radiosurgery in brain lesions is well established, nevertheless, its use for multiple lesions remains as exceptional and carefully indicated according to the current literature. Perhaps our number of patients seems to be representative of this controversial indication. Regarding both the selection criteria for this study and the quality of care provided by our institution, we included all consecutive patients in this period, all evaluated in a retrospective fashion as described. We decided to use this period (30 months) as a representative timeframe to detect overall and specific outcomes regarding toxicity. The study was approved and performed in accordance

with the Institutional Review Board, and we understood that neither a bigger sample nor a longer period would bring more clarity to this question and, perhaps, keep more patients under treatment without assessing their risk of toxicity in deeper analyses. Our results did not change our practice since their represented acceptable toxicity when compared who underwent treatment for fewer lesions, but certainly it would if it represented unmanageable toxicity. We do appreciate your concerns, and we added the word in the methodology section to clarify that all patients in the period were included.

Point 2 - Table 1 - 53 patients? --> should this be 55 patients? please check this. or otherwise make this clear in the patient selection section.

Point 3 - Table 1 - KPS is 34, but there are 35 patients? why is 1 missing? please look into this!

Answer (for both points 2 and 3): Thank you so much for your attentive review, we appreciate it. As described in our previous answer, we included all consecutive patients in the period. We had a total of 55 patients, 35 in the non-previous irradiation group and 20 in the previous irradiation group, but due to the retrospective nature of the study, unfortunately, it was not possible to assess enough information for two patients, thus, the number decreased for 53 patients, as demonstrated in Table 1. Although we understand this missing information as a limitation of our study and a common risk of bias for retrospective studies, it represents only 3.7% (2/55 patients), and it does not seem to invalidate our data, and acceptable for retrospective studies [1]. The same obstacle explains the fact that we have 34 patients with complete information about the KPS among the 35 patients in the group NP (2.8% of missing data for this variable). We added sentences in the methods and discussion sections to reinforce these limitations and address your concerns, and we believe that the new version is clearer for the readers and their critical appraisal. Otherwise, if you think

that is not comprehensive yet, let us know about it and we can change as much as necessary to deliver a clear message about it.

Point 4 - Also the two groups do not contain an equal amount of patients. It doesn't feel like a good comparison, also taking into account point 2 and point 3.

Answer: Regarding the unbalanced number of patients, probably is just a reflection of the retrospective nature of this study. Addressing your concerns about the unequal number between the groups occasionally compromising the obtention of “a good comparison” seems to be inaccurate considering the methodological and statistical points of view. As much as we know about the methods and biostatistics in clinical research, an equal number of patients into groups as mandatory to obtain a fair comparison is neither necessary nor a guarantee of trustable evaluation for measuring association among variables [2, 3].

It is always impossible to reject the risk of facing a type II error for a limited number of patients, yet it would not be expected as a consequence of unbalanced distribution. Moreover, as we answered in your first comment, we included all consecutive patients, and if we decreased the number of patients included to achieve an apparent balance, it would either represent an important risk of selection bias and a higher risk for a type II error.

Nevertheless, if you think that this point (unbalanced distribution of patients) represents a possible drawback for our study, we will kindly ask you to clarify your concerns about this specific issue and we will be happy to adjust our manuscript to address this point. We appreciated your attentive review of our manuscript and your meaningful suggestions for increasing its quality, and we also requested an English

edition for an authorized professional in the field. Thank you for your patience and for the opportunity to review our manuscript, we appreciate it.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors:

Point 1 - Are both groups suitable for comparison (age, gender, diagnosis, location, and number of metastases)?

Answer: Thank you so much for your meaningful comment, we appreciate it. We do believe that your suggestion will increase the quality of our paper, and we are remorseful because we did not make it clear in the original submission. We both included the p values in Table one and addressed the results in the results and discussion section.

Point 2 - Have the patients received other treatments other than SRS (radiotherapy or chemotherapy)?

Answer: Yes, all of them received some or many kinds of local and systemic treatment for the many types of tumors, since in our institution the radiosurgery for 4 or more lesions was reserved for local control in a palliative manner and usually failed for previous treatments. Considering that we approached many types of cancers and our primary outcome was toxicity, we did not describe the previous modality since we

faced a huge heterogeneity and long-term outcomes were minor outcomes in our retrospective series. We previously addressed this point.

Point 3 - Has SRS always been applied by the same researchers? Initials of their names should be given in the method section.

Answer: Thank you for your question and welcome suggestion. The answer is that many providers from the Department of Radiation Oncology work on both the planning and execution of the treatment and not all of them are included here as co-authors. Nevertheless, we appreciate your suggestion, and we included the initials of the co-authors in the manuscript as representatives of a team of the Department of Radiation Oncology.

Point 4 - Has a multivariate analysis been performed to eliminate confounding factors?

Answer: Thank you for your meaningful question. We did not include a multivariate analysis for two combined principals, we are facing a heterogeneous population in a small sample which would represent a risk for failure in the detection differences among groups. A multivariate model requests a minimal number of events of interest per variable. Usually, the minimum number of events per variable should be 10 to 15; if this is not reached, only univariate analysis alone should be performed, dismissing the multivariate model [4, 5, 6]. In our study, the univariate analyses for previous or not treatment were non-significant. Thus, only univariate analysis was presented, and confounding bias cannot be excluded, but we included those considerations in the

discussion section to make it clearer. Thank you for your helpful observation, we believe that its elucidation increased the quality of our paper.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Minor revision

Specific Comments to Authors: *An interesting and meaningful study on evaluating the effect of isolated radiosurgery treatment on patients with multiple brain metastases (four or more lesions). The authors retrospectively collected data of the eligible study population in a single institution (N = 55). The Spearman's rank coefficients, Mann-Whitney test, Kruskal–Wallis test, and Log-rank test were conducted. Although interesting and meaningful, there are some problems in the manuscript.*

Point 1 - Line 65-66, there seems to be some typing omissions in “10 months (8.9 months)” and “3.6 months for KPS 70 (P = 0.047)”.

Answer: Thank you very much for your attentive review, we appreciate it. Sorry about the miss-typed information in the abstract. The median overall survival of patients with KPS > 70 was 8.9 months, as was described in the manuscript. We fixed the abstract (highlighted in yellow)

Point 2 - There is necessary to perform appropriate statistical tests on all the results and add corresponding p-values in the presentation of the results.

Answer: Thank you for your constructive observation, we are sorry for this missing information, and now we added the appropriate tests in the manuscript, more precisely in Table 1.

Point 3 - The population of this study is small and the results could be more convincing if including more patients from another institution.

Answer: We totally agree with your comment, and it would be pretty much appreciated. Nevertheless, it was not possible since this project was part of a postgraduation project within a short period of time, looking for the internal validity (and safety of our patients) of the use of radiation surgery for 4 or more brain lesions, as approved and performed in accordance with the Institutional Review Board. We decided to use this period (30 months) as a representative timeframe to detect overall and specific outcomes regarding toxicity for our population, and neither a bigger sample nor a longer period would add more information for these specific goals. Moreover, considering the usual palliative aim of this therapy, in high select patients, it seems unpractical uses in our country at least.

Point 4 - For brain metastasis in the Introduction and Discussion parts, some important ref. must be cited, such as, PMID 36991428, 36529697.

Answer: Thank you so much for your suggestions, we added sentences in both the introduction and discussion using these references (references 2 and 3).

References:

1. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J.
Methodological index for nonrandomized studies (minors): development and validation of a new instrument. ANZ J Surg. 2003;73:712–6.
2. Paolino, B.S., Araújo, R.L.C., Bristol, D. (2018). Testing Measures of Associations. In: Araújo, R., Riechelmann, R. (eds) Methods and Biostatistics in Oncology. Springer, Cham. https://doi.org/10.1007/978-3-319-71324-3_4
3. R. L. C. Araújo, R. P. Riechelmann (eds.), Methods and Biostatistics in Oncology, © Springer International Publishing AG, part of Springer Nature 2018 1, doi.org/10.1007/978-3-319-71324-3_1
<https://link.springer.com/book/10.1007/978-3-319-71324-3>
4. Bagley SC, White H, Golomb BA: Logistic regression in the medical literature: standards for use and reporting, with particular attention to one medical domain. Journal of clinical epidemiology 2001;54:979-985.
5. Peduzzi P, Concato J, Kemper E, et al.: A simulation study of the number of events per variable in logistic regression analysis. Journal of clinical epidemiology 1996;49:1373-1379.
6. Araújo, R.L.C., Riechelmann, R.P. (2018). Interpretation of Results from Tables, Graphs, and Regressions in Cancer Research. In: Araújo, R., Riechelmann, R. (eds) Methods and Biostatistics in Oncology. Springer, Cham. https://doi.org/10.1007/978-3-319-71324-3_6