Reviewer's report

Title: Prognostic factors for outcomes after whole-brain irradiation of brain metastases from relatively radioresistant tumors: a retrospective analysis

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Reviewer: Gustavo Viani

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Dear editor

Rades D et al. in the manuscript entitled ``Prognostic factors for outcomes after whole-brain irradiation of brain metastases from relatively radioresistant tumors: a retrospective analysis`` described the outcomes and prognostic factors in 220 patients with relatively radioresistant tumors (colon, melanoma and renal cancer). In that article those patients were treated with whole brain radiotherapy using different schedules of radiotherapy. Beside of that, the authors have evaluated the influence of prognostic factors on overall survival and local control. The results show that in the multivariate analysis, WBI doses >30 Gy, KPS #70, only 1-3 brain metastases, lack of extracerebral metastases, and RPA class 1 were associated with improved survival. The local control rates at 6 and 12 months were 37% and 15%, respectively. In the multivariate analyses of local control, KPS #70, only 1-3 brain metastases, and RPA class 1 were associated with improved local control.``

As conclusion the authors affirm that the improved outcomes were associated with WBI doses >30 Gy, better performance status, fewer brain metastases, lack of extracerebral metastases, and lower RPA class. Carefully selected patients with relatively favorable prognoses may receive neurosurgery or radiosurgery in addition to WBI. Patients treated with WBI alone appear to benefit from WBI doses >30 Gy.`` For me the results of that article bring important conclusions regarding the palliation treatment in patients with brain metastases from these tumors. However, it needs to be substantially edited before publication.

Below follow major compulsory revisions:

Introduction

In the first paragraph the authors affirm ``Little data exist regarding the radiotherapy of brain metastases from such tumors.`` In the other paragraphs they described other options of treatment, the importance of the radiotherapy doses and the prognostic factors for survival. But, at no time, they relate or appreciate the objectives of study with the data cited. Thus, I suggest that the author rewrite the introduction given value to ``Little data exist regarding the radiotherapy of brain metastases from such tumors.``

The method section

It is well written. But, I suggest that the authors describe which radiotherapy treatment technique and machines were used in each institution.
Results
This section also it is well written. However, when we used multivariate analysis with Cox regression methods, the result are not described as risk ratio. The Cox methods describe the hazard of an event to occur in a period of time. So, I suggest rewriting it as hazard risk.

Moreover, WBI with total dose > 30 Gy was associated with better survival. So, the authors concluded that patients who are treated with WBI alone appear to benefit from an escalation of the WBI dose beyond 30 Gy. But, that result is valid for all patients. For example, patients with poor performance status or RPA class 3, would benefit from a long course of radiotherapy fractionation? What is more important for overall survival in those tumors; the fractionation, total dose or BED?

Discussion
The first paragraph is not necessary
`` WBI alone still is the most frequently used treatment for brain metastases. In patients with a relatively favorable survival prognosis, WBI may be supplemented with more aggressive approaches such as neurosurgery or radiosurgery. If neurosurgery is performed, it usually has to be aggressive, as surgical removal appears to improve survival if all metastases are completely removed [12]. Craniotomy always entails certain surgery and anesthesia related risks. Radiosurgery is less invasive than neurosurgery. However, it is generally reasonable only in patients with a limited number of cerebral lesions. Radiosurgery may lead to intracerebral hemorrhage, in particular in melanoma or renal cell carcinoma patients [13,14]. On the other hand, neurosurgery and radiosurgery may improve survival in patients with a few lesions when compared to WBI alone.``

What the importance and relation of this paragraph with your cohort and your results?

In the fourth paragraph the authors affirm `` The biological effectiveness of irradiation depends on both the total dose and the dose per fraction. Different radiation schedules can be compared with the Equivalent Dose in 2 Gray Fractions (EQD2), which takes into account both the total dose and the dose per fraction [18]. The EQD2 is calculated with the equation \( \text{EQD2} = D \left( \frac{(d + #/#)}{(2 \text{ Gy} + #/#)} \right) \), as derived from the linear-quadratic model; \( D \) = total dose, \( d \) = dose per fraction, \( # \) = linear (first-order dose-dependent) component of cell killing, \( #/# \) = quadratic (second-order dose dependent) component of cell killing, \( #/#\)-ratio = the dose at which both components of cell killing are equal. Assuming a \#/#-ratio of 10 Gy for tumor cell kill, the EQD2 of the radiation schedules are 23.3 Gy (5x4 Gy), 32.5 Gy (10x3 Gy), 40 Gy (20x2 Gy), and 48.8 7 Gy (15x3 Gy), respectively. Our data suggest that administration of higher doses may overcome relative radioresistance and improve overall survival.``

Again, What the objective of the authors with that paragraph? Maybe, the goal would be to demonstrate the radioresistant of those tumors?
However, to assume #/#-ratio of 10 Gy for tumor cell kill is completely wrong. Because those tumors are assumed to be radioresistant, the corrected #/#-ratio is of 3 Gy for tumor cell kill. I think that the paragraph must be rewritten, highlighting that schedules of fractionation achieving BED higher than xx Gy3 resulted in better survival.

Moreover, I suggest that the authors introduce in this section a table, resuming the results of other similar series.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.