Clinical and Translational Radiation Oncology 48 (2024) 100826

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

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Reply to: Comment on "Repeated HyperArc radiosurgery for recurrent intracranial metastases and dosimetric analysis of recurrence pattern to account for diffuse dose effect on microscopical disease"

The interesting letter from Di Perri permit us to discuss more extensively the findings of our study and future clinical application of brain RT [1]. The management of brain metastases (BM) significantly evolved in the last years with the introduction of systemic agents and precise RT technology that are allowing to administer effective treatments with limited side effects.

In this regards, mono-isocentric techniques are very appealing for treating simultaneously multiple BMs. On one hand, they permit very steep dose gradient with limited toxicity, an important reduction in the time required for patients, treatment slots and costs [2,3], on the other hand they carry with them inevitably a certain diffuse low dose to the healthy brain.

Several evidence already documented the role of low radiation dose in controlling the microscopic disease, so we hypothesize how to exploit this inevitable and peculiar characteristic of monoisocentric technique to obtain a clinically relevant effect. In particular:

1) Being aware that low dose isodoses have had a larger volume than high dose isodoses, we corrected the number of BMs per isodose volume, as already explained in methods section (n° of new BMs/ isodose level volume) [1]. So the dose of 7 Gy resulted corrected per isodose volume and truly representative of low radiation dose effect.
2) The effect of intracranial failure after WBRT should be weighted with the extracranial disease control. In fact, systemic progression might also determine a new intracranial metastatic wave [2]. Therefore, we included only patients without systemic progression after HyperArc to exclude systemic progression as a potential source of new BMs. Moreover, In the *meta*-analysis from Sahgal et al. [4] the risk of intracranial relapse between SRS and SRS + WBRT was not significantly different for patients $\leq$ 50 years and the difference was observed only in those $>$ 50 years. Also, a study from Nakano et al. showed that a dose reduction to the brain was not associated with increased brain failure [5]
3) Apart from preclinical studies, there are several trial clinically addressing the effect of low RT dose to the hippocampi. Even if results regarding hippocampal-avoidance (HA) technique are not definitive yet [6], it was demonstrated the possibility to positively impact on neucognitive function. For example, the phase II trial RTOG 0933 demonstrated that a dose to the 100 % of the hippocampi not exceeding 9 Gy during WBRT might preserve neurocognitive function [7]. The phase II trial of Westover et al. used a treatment concept more similar to that proposed in our paper: a lower WBRT dose (20 Gy/10 fx) with a boost of 40 Gy to the BM and a hippocampi dose not exceeding 16 Gy. The results showed only a 10.6 % mean decline in verbal memory performance without sacrifing intracranial control [8].

Despite the limitations of a retrospective study, we believe that the strategy of low-dose WBRT plus SRS/SRT could be proposed to long-surviving patients especially in those where systemic drugs permit a long-lasting disease control and where the early resort to WBRT might be detrimental for their quality of life.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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https://doi.org/10.1016/j.ctro.2024.100826
Received 18 July 2024; Accepted 24 July 2024
Available online 27 July 2024

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