Author's response to reviews

Title: Hypofractionated stereotactic re-irradiation: treatment option in recurrent malignant glioma

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Author's response to reviews: see over
Dear Dr. Newmark:

Thank you for the opportunity to revise our manuscript entitled “Hypofractionated stereotactic re-irradiation: treatment option in recurrent glioma” according to the reviewers’ recommendations.

Please, find below the point-by-point response to the comments. A revised version of the manuscript and figures are attached.

Sincerely,

Dirk Vordermark, MD
Response to review by B. Baumert:

This reviewer recommends minor essential revisions:

1. The term “focal” was replaced by the term “involved-field”.

2. The reviewer requests information on the choice of margins (1 mm to 3 mm). As the time period during which patients were treated is rather long (six years), several different radiation oncologists were involved in the treatment of these patients. During this time, new information on the isocenter reproducibility with non-invasive fixation for stereotactic radiotherapy become available, e.g. from our institution (Ref. 10). It is not possible to justify, in retrospect, the choice of margins in individual cases. For hypofractionated treatments (such as 6 x 5 Gy) without CT verification before each fraction we would now choose 3 mm.

3. The dose ranges for corticosteroids were indicated as stated since dexamethasone is known to have approximately 7-fold glucocorticoid potency of prednisolone such that doses can be compared between different corticosteroid substances.

4. The term “borderline significance” with respect to the effect of total dose on overall survival was replaced by “trend” (p=0.051) in the manuscript and also eliminated from the abstract.

5. The justification for choosing 30 Gy and <30 Gy total dose as a cut-off point for statistical analysis is to generate groups of similar size for comparison. As shown in Table 2, essentially 42% received 20 Gy (in different fractionation schemes) and 58% received 30 Gy.

6. Similar to the margins (see above) the choice of fractionation cannot be explained in retrospect. It should be noted that during the time of investigation new information on fractionation and total dose in this situation became available, favoring more intensive treatment with doses such as 6 x 5 Gy.
The format of the tables was left as is for now, changes at the discretion of the editor.

For all comparisons (Table 3) the intention was to use the median as cut-off point (e.g. for planning target volume). This was not always possible, as only 5 of 19 patients, for instance, had a Karnofsky performance score of less than 90.

A useful analysis of fractionation schemes in this setting, e.g. 5 x 4 vs. 4 x 5 Gy, was not possible due to the small sample size. Therefore, only total dose was analyzed.

The language suggestions were implemented as recommended.
1 The reviewer criticizes the lack of a definition of tumor progression after HFSRT. Imaging was not reviewed using uniform criteria for the purpose of this analysis. The neuroradiological diagnosis of tumor progression, based on progressive contrast enhancement on CT or MRI, was considered for the analysis. Imaging was routinely reviewed by an interdisciplinary tumor board and further treatment recommendations were based on these findings. In case of uncertainty (tumor progression vs. radionecrosis), 1-H MRI spectroscopy was recommended. However, no patient was eventually diagnosed with symptomatic radionecrosis or had predominant radionecrosis on histology at reoperation. The approach regarding tumor progression is clarified in the revised version.

2 Overall survival times from first diagnosis by initial histological grade were added in the results section.

3 The reviewer is concerned about the inclusion of pediatric patients in the analysis. In fact, the patient described in detail was the only such patient. The second youngest patient was 31 years old at the time of re-irradiation. This issue is clarified in the revised version.