Re-irradiation of brain tumours – evidence, indications and limitations

S.C. Short

University College London, London, UK

Historically, radiation-oncologists have been cautious about re-irradiating brain tumours because of concerns about the risk of late toxicity, particularly radionecrosis, which can occur several months to many years following treatment. The pathogenesis of radiation induced necrosis is still debated but is probably a combination of vascular and glial cell damage that is related to both total dose and the volume treated [1]. Available animal data come mainly from studies investigating spinal cord tolerance and suggest that the time between radiation exposures is also relevant to the risk of necrosis, and that up to 50% recovery may occur within 1–2 years post initial treatment if doses below full tolerance have been given at first exposure [2]. It is not clear if the same constraints apply to the brain, where most of the data come from clinical series [3].

The currently available clinical data sets describing outcomes after re-irradiation in glioma are retrospective and have used a variety of radiotherapy doses, techniques and volumes highlighting the fact that no standard approach to re-irradiation exists in this context. Nevertheless, the available clinical data suggest that re-irradiation may be a relatively safe and effective approach in well-selected patient groups [4–9]. In the largest published data set, hypo-fractionated re-irradiation was associated with median survival times of 5 months post treatment, which compares well to outcomes after second or third line chemotherapy regimes [7]. In the only reported case-control study comparing re-irradiation with chemotherapy, it was suggested that response rates may be at least as good as with systemic treatment with nitrosureas [5]. These data need to be compared with expected outcomes in this patient group; a recently published evaluation on prognostic factors for patients with a recurrent high-grade glioma based on 10 prospective phase I or II trials resulted in a recursive partitioning analysis (RPA) consisting of seven prognostic subgroups [10]. The best group of patients with a recurrent glioblastoma multiforme has a median survival of 10.4 months, the middle group of approximately 6 months. Relevant prognostic factors are performance status, age and steroid intake. Most recent data assessing response to re-irradiation using either radiosurgery or fractionated stereotactic radiotherapy report a median survival of around 8 months, with radiological response rate of 40% based on magnetic resonance imaging criteria [11].

A systematic review of 21 studies of the effects of re-irradiation of brain tumours was recently published by Mayer and Sminia [12]. This review excluded patients treated with brachytherapy, but sought to evaluate outcome in cohorts treated with fractionated external beam or radiosurgery approaches. 21 studies were included but the authors acknowledged limitations in the data since details of important variables including time between radiation courses and treatment volumes were rarely available. They also make the point that the incidence of toxicity, including radionecrosis, may be significantly under-reported in these data sets since only symptomatic necrosis is likely to be recorded. The definition of true normal tissue necrosis, as opposed to tumour recurrence associated with necrosis, is also an unresolved issue and there remains no gold standard imaging modality to resolve this, hence only patients with symptoms requiring further surgery can be diagnosed with any certainty. In this review the major factor contributing to the risk of necrosis was the total dosage received. No correlation between the time interval between the initial and re-irradiation course and the incidence of radionecrosis was noted; the minimum interval between treatments was 3 months. Necrosis did not increase significantly unless the total cumulative dose from the first and second irradiations was greater than 100 Gy. High-precision radiotherapy using a greater single-fraction dose did not increase the risk of brain necrosis despite larger doses often being used in this context. Since these are retrospective data they cannot address the relative importance of these variables with any certainty, but this work again suggests that re-irradiation can be given safely using a variety of techniques.

The available treatment options for recurrent high-grade gliomas have increased significantly in the last

few years with the introduction of new molecular targeting approaches. In the next few years the utility of these agents in patient groups defined by specific biomarkers of response will become available. In most cases though, these agents are likely to produce cytostatic effects, hence they will need to be given in combination with conventional cytotoxics. Since current standard first line treatment includes temozolomide chemotherapy in a high proportion of these patients, such combinations may be limited by reduced bone marrow reserve as a result of previous treatment. In these circumstances the use of re-irradiation may have important advantages since it avoids any systemic side effects. There are also some intriguing data that suggest that the combination of some of these agents with radiation may improve the therapeutic ratio. For example, Wong and colleagues have suggested that the use of bevacizumab (Avastin) can reverse radiation induced necrosis in the central nervous system [13]. Combination of bevacizumab with re-irradiation for glioma has recently been demonstrated to be practical [14]. If these data are confirmed in larger studies, the use of highly targeted radiotherapy in combination with similar agents will become more appealing.

Our understanding of the tolerance of the brain to re-irradiation for brain tumour patients is evolving. This approach is attracting more interest because of developments in radiotherapy technology and imaging that make highly accurate targeting of biologically relevant tumour volumes possible. In the era of molecular targeted therapy, irradiation is likely to remain an important adjuvant treatment and further exploration of the role of re-irradiation as a single modality or in combination with novel agents is warranted.

Conflict of interest statement

None declared.

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