Review Article

Re-irradiation for recurrent glioblastoma multiforme

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Abstract: As our understanding of normal brain tissue tolerance and radiation technology have improved, central nervous system (CNS) re-irradiation has garnered more attention; whereas, in the past there had been hesitancy due to late toxicity concerns, particularly radionecrosis (RN). There is minimal prospective data evaluating repeat radiation in recurrent gliomas. In this review, the rationale for and different approaches to re-irradiation will be discussed, and the biology and clinical impact of late CNS toxicity will be reviewed.

Keywords: Re-irradiation; glioblastoma; radionecrosis (RN); imaging

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Introduction

The use of radiotherapy (RT) is standard in the management of newly diagnosed glioblastoma multiforme (GBM), whether in the postoperative or primary treatment setting, with temozolomide (TMZ) typically given during and after RT. Unfortunately, the large majority of patients develop intracranial recurrence, most often within or just outside the high-dose radiation field (1,2). Treatment options in the setting of local recurrence include supportive care, re-resection, re-irradiation, systemic therapies, or a combination approach.

Diagnosis of recurrence

Radionecrosis (RN) and recurrent tumor are often indistinguishable by magnetic resonance imaging (MRI) and present with similar neurological symptoms, making the diagnosis of local recurrence in GBM difficult. A combination of diffusion- and perfusion-weighted MRI can improve diagnostic accuracy by exploiting differences in tissue cellularity and microvasculature respectively (3). For example, a low apparent diffusion coefficient in a hyperintense lesion is characteristic of tumor recurrence whereas low cerebral blood flow and volume are characteristic of RN. Additional functional imaging including magnetic resonance spectroscopy (MRS), single photon emission computed tomography (SPECT) or positron emission tomography (PET) can help better characterize the biology of the lesions, though each of these modalities has their limitations.

MRS characterizes tissues using ratios of choline (Ch), creatinine (Cr) and N-acetylaspartate (NAA); high Ch/NAA (>1.11) and Ch/Cr (>1.17) ratios and a low NAA/Cr ratio are typically seen in tumor recurrence. Results for MRS are wide ranging, with reported sensitivities and specificities of 61–94% and 82–100%, respectively (4-7). These inconsistent results are largely due to differences in spectroscopy, a factor that should be considered during clinical decision making. For instance, single-voxel MRS only samples at one location, possibly mischaracterizing a heterogeneous entity such as recurrent GBM, whereas multivoxel MRS obtains samples throughout a lesion, better defining spatial heterogeneity (7).

Tracer dependent studies (SPECT, PET) are mostly limited by poor spatial resolution, steroid use, and significant normal tissue tracer uptake (8). Fluorodeoxyglucose (FDG)-PET in particular displays this issue given the elevated

glucose metabolism in normal brain tissues. A search continues for highly sensitive and specific alternatives to FDG that do not accumulate within the normal brain parenchyma. Some promising candidates remain under investigation such as fluoroethyltyrosine (FET), fluorothymidine (FLT), fluoro-dihydroxyphenylalanine (FDOPA) and other amino acid analogues; however, none are widely available to date.

The Response Assessment in Neuro-Oncology criteria are the current standard for treatment response assessment and definition of tumor recurrence used for the majority of clinical trials. The application of these criteria have been previously described (9).

Summary of non-RT options for recurrent glioblastoma

There is minimal data from randomised controlled in the treatment of recurrent GBM. As mentioned, treatment options for recurrence have typically included further surgery, systemic therapy, and more recently re-irradiation, but currently, there is no established standard of care.

Further neurosurgical intervention may be limited by the infiltrative nature of these tumors, and is usually avoided in the presence of multifocal disease or when eloquent tissues are involved. Novel resection techniques are also being explored to improve the rate of complete resection. For example, protoporphyrin IX (PpIX) is a fluorescent compound that preferentially concentrates in malignant glioma cells, allowing for successful intra-operative tumor visualization to guide surgical resection (10,11). Despite such advances, the principle of maximum safe resection is not always optimal in the setting of recurrent GBM, as the benefit of reoperation remains in question (12-14). In general, surgery seems to be most beneficial when there is a discrete, well-defined lesion in a non-eloquent location and resection is expected to relieve symptomatic mass effect. Placement of resection cavity carmustine wafers can afford a modest improvement in survival as well (15). Repeat resection should be offered in the setting of discrete, resectable disease.

A comprehensive review of all trials investigating different systemic therapies for the treatment of recurrent GBM is beyond the scope of this review, however, a brief history and important recent results will be discussed to give context to re-irradiation decision making. In 1998 Huncharek and Muscat authored a systematic review of 40 trials evaluating earlier outcomes in recurrent high-grade gliomas; seven were RT trials and the remainder addressed cytotoxic chemotherapy outcomes (16). In their review, nitrosoureas were associated with significantly improved time to progression (26.9 weeks), with the use of nitrosoureas or platinum agents found to improve overall survival (OS) as well (32 weeks). Average median survival for patients receiving re-irradiation was 44.7 weeks. Comparisons were not made between chemotherapy and RT studies given the inherent selection bias. Since then, more systemic agents have emerged, the most studied of which are TMZ and bevacizumab. No single or combination drug therapy has shown obvious survival superiority, thus, there is no standard regimen for GBM in the recurrent setting. Although, bevacizumab is most often utilized due to improvement in progression free survival (PFS) and its anti-steroidal effects improve symptoms in many patients.

The biology of late neurotoxicity

When considering treatment options for recurrent glioblastoma, one must balance the efficacy with the toxicity of each option, especially in view of the relatively poor prognosis. Three phases of toxicity are normally considered following central nervous system (CNS) irradiation—early (days to weeks), early delayed (1 to 6 months) and late (>6 months). Early toxicity is often self-limited or managed conservatively, but late toxicity is typically progressive and irreversible.

Demyelination, microvascular changes, and necrosis are the pathologic hallmarks of late injury. This injury is considered a multifaceted process, involving various cell types and interactions. Given this complexity, efforts to devise effective preventive or treatment strategies have been unsuccessful to date (17,18). However, conservative estimates based on animal and other preclinical data suggest that the spinal cord and perhaps other CNS normal tissues may recover up to 60% from sub-tolerance doses over 1–3 years (19). Normal tissue complication models in rats have also suggested that the CNS behaves as a serial structure (20). As such, the toxicity of re-irradiation is likely also dependent on volume irradiated, in addition to dose and time interval to re-treatment. Modern re-irradiation techniques are capable of optimizing these parameters so as to reduce the risk of clinically apparent late toxicity.

Patient selection for re-irradiation

Individual patient and tumor characteristics should be used to estimate prognosis and tailor management in the recurrent

setting. In 2007 Carson *et al.* (21) defined seven prognostic groups in patients with recurrent high-grade glioma by performing recursive partitioning analysis (RPA) of data from ten phase I and II trials. Significant prognostic factors for recurrent GBM were age (>50), Karnofsky performance status (KPS >90 *vs.* 60–80), and baseline steroid requirement. A similar study reviewing data from 300 patients with recurrent GBM recruited in eight phase I or II trials conducted by the European Organization for Research and Treatment of Cancer (EORTC) showed poor performance status (PS) and >1 target lesion were prognostic for decreased PFS and OS. Lesions ≥4.2 cm and baseline steroid requirement were also associated with shorter OS whereas frontal tumor locations conferred a survival advantage (12). In patients undergoing fractionated stereotactic radiation (FSRT) for re-irradiation of high-grade gliomas, Combs *et al.* showed that a time to re-irradiation <12 months negatively impacted survival (22). A combination of these data can help individualize the potential benefits of re-irradiation and guide patient counselling.

The decision for retreatment should only be made when the risks are outweighed by potential benefits of treatment. High-dose brain irradiation can have a number of side effects that can substantially impact quality of life (QOL) including focal neurologic deficits, seizure, memory and/or cognitive impairment, and personality change. In the event of RN, reoperation is often necessary. Due to a paucity of data addressing QOL in GBM retreatment, extrapolations from primary treatment of GBM can be made. Prospective trials in primary treatment of GBM have correlated poor post-treatment QOL and symptom burden with decreased rates of survival (23,24). This data further underscores the importance of patient selection for re-irradiation.

Evidence for re-irradiation

Numerous institutions have reported their re-irradiation disease control and toxicity outcomes (*Table 1*). Almost all reports are retrospective in nature and as such there is little consistency in treatment technique, total dose, and volume treated. These differences make it difficult to establish a standard approach to re-irradiation. Regardless of the methods used, prognosis remains poor with median survival ranging from 7–15 months (*Table 1*).

Conventionally fractionated radiotherapy

In multifocal, diffuse, or unusually large recurrent tumors, a more generous treatment volume may be required. In contrast to stereotactic radiosurgery (SRS) or hypofractionated stereotactic RT (HFSRT), the smaller fraction sizes associated with conventional fraction may allow for treating larger target volumes while still maintaining acceptable rates of toxicity. For example, with a median time between primary RT (median 60 Gy) of 10 months, Combs *et al.* retreated 172 high-grade gliomas (GBM =59) to a median dose of 36 Gy in 2 Gy daily fractions using 0.5–1 cm margin. Median survival after re-irradiation for the GBM group was 8 months and only one patient developed RN.

SRS and HFSRT

When recurrences are discrete and retreatment volumes small, HFSRT and SRS can be considered. These methods offer certain technical and dosimetric advantages compared to conventional fractionation, while also affording the patient-friendly benefit of consolidating re-irradiation into fewer days.

The high accuracy and conformality associated with SRS allows for delivering a high dose of radiation to a brain lesion in a single outpatient treatment. The steep SRS dose gradient is best suited for discrete recurrences or when there are nearby critical CNS structures. In FSRT, the dose is divided into several semi high–dose fractions; this offers the radiobiologic advantage of allowing normal tissues to heal between fractions, thus reducing the potential for normal tissue toxicity compared to single fraction treatment. As such, this technique is often useful when the target volume is felt to be too large for SRS, or when single fraction normal tissue constraints cannot be met because the target is located too close to a critical structure.

Both SRS and FSRT have been shown to be effective with similar rates of toxicity (*Table 1*), as such there is currently no standardized preference for one over the other in the recurrent GBM setting. In a more recent study, Patel *et al.* treated 38 GBM patients with either SRS (single 18 Gy fraction) or FSRT (36 Gy in 6 Gy fractions) with reported median survivals of 8.5 and 7.4 months respectively and a radiological response rate of 40%. Pathologically confirmed RN was found in 2 SRS and 1 FSRT patients (34). The National Cancer Institute has an ongoing HFSRT dose escalation trial (NCT02709226) which should provide much needed re-irradiation dosimetric and toxicity data that can serve as a framework for future clinical trial design.

Treatment fields

Gadolinium enhanced, thin-sliced MRI remains the standard

Table 1 Summary of the largest re-irradiation studies for patients with recurrent glioblastoma multiforme (GBM)

Author	Number treated (GBM)	Technique and regimen	MS	Toxicity
Brachytherapy				
Scharfen 1992 (25)	66	LDR, I-125, 64.4Gy	11.3	7.9% grade ≥3
Patel 2000 (26)	40	LDR, I-125, 120–160 Gy to 5 mm	10.8	No RN, 1 infarct
Gabayan 2006 (27)	81	LDR, GliaSite, 60 Gy at 10 mm	8.4	2 patients with RN
Tselis 2007 (28)	84	HDR, Ir-192 40 Gy	8.6	6% grade ≥3: RN (n=2), hemorrhage (n=3, 1 death)
Darakchiev 2008 (29)	34	LDR, I-125, 120 Gy to 5mm	15.9	8 patients with RN
SRS				
Shrieve 1995 (30)	86	SRS, 13 Gy	10.2	22% required reoperation for refractory RN
Cho 1999 (31)	46	SRS, 17 Gy	11.0	30% RN in SRS group
Combs 2005 (32)	32	SRS, median 15 Gy (10–20 Gy)	10.0	No grade ≥3 toxicities
Kong 2008 (33)	65	SRS, 16 Gy	13.0	24.4% radiographic RN
Patel 2009 (34)	36	SRS, 18 Gy FSRT, 36 Gy in 6 fractions	8.5 7.4	Pathologically confirmed RN in 2 SRS and 1 FSRT patients
Cuneo 2012 (35)	49	SRS, 15 Gy	10	6 patients with RN
HFSRT				
Lederman 2000 (36)	88	HFSRT, 24 Gy in 4 fractions	7.0	11 patients required reoperation for refractory RN
Grosu 2005 (37)	44	HFSRT, 30 Gy in 6 fractions	–	No grade ≥3 toxicities
		36 PET/SPECT	9.0	–
		8 CT/MRI	5.0	–
Fokas 2009 (38)	53	HFSRT, 30 Gy in 10 fractions	9.0	No grade ≥3 toxicities
Fogh 2010 (39)	105	HFSRT, 35 Gy in 10 fractions	11.0	No reoperations, 1 late grade 3 toxicity (headache)
CFSRT				
Arcicasa 1999 (40)	31	CFSRT, 34.5 Gy in 23 fractions	13.7	No late CNS toxicities
Cho 1999 (31)	25	CFSRT, 37.5 Gy in 15 fractions	12.0	8% RN in CFSRT group
Combs 2005 (41)	59	CFSRT, 36 Gy in 18 fractions	8.0	No grade ≥3 toxicities
Kohshi 2007 (42)	11	CFSRT, 22Gy in 8 fractions (+ hyperbaric oxygen)	11.0	2 patients required reoperation for refractory RN

Abbreviations: HSFRT, hypofractionated stereotactic radiotherapy; SRS, stereotactic radiosurgery; MS, median survival; GBM, glioblastoma multiforme; LDR, low-dose rate; HDR, high-dose rate; RN, radionecrosis; CFSRT, conventionally fractionated stereotactic radiotherapy; CNS, central nervous system.

imaging modality for target definition. New or progressive contrast-enhancing lesions should be delineated as gross tumor volume. The use of a rigid head frame and same-day imaging for target delineation can minimize geometric and image fusion error, thereby reducing the need for PTV expansion. When applying these principles for SRS or HFSRT, elimination of PTV expansion can be considered; however, a small 1–2 mm margin may be added based on physician preferences. Ideally, adequate head immobilization should be used to where PTV expansion is at most 5 mm.

Brachytherapy

Similar to SRS or FSRT, brachytherapy allows for a

sharp dose gradient with placement of a radiation source within the treatment volume. This is typically done in the postoperative setting, and, as such, patients selected for brachytherapy are usually those with good PS who have small-volume, resectable tumors. Different approaches include placement of permanent iodine 125 (I-125) seeds or a temporary intracranial balloon catheter filled with an I-125 containing solution in the resection cavity. A number of retrospective studies have reported favorable outcomes with median survival times of 8.4 to 15.9 months (*Table 1*). It should be noted, however, that comparisons to other re-irradiation modalities should be made with caution given the selection biases mentioned above. One disadvantage of brachytherapy is that the effectiveness and toxicity of treatment is highly dependent on the quality of implant; accordingly, high re-operation rates and RN incidence have been reported (*Table 1*).

Conclusions based on clinical evidence

Considering the variety of techniques and disease/toxicity outcomes discussed above, it is no wonder that despite a large body of clinical work, no standard practice exists for re-irradiation of GBM. Prospective data and clinical trials are needed to eliminate the many confounding factors inherent in retrospective studies. Despite these limitations, the existing data suggests that with thoughtful patient selection, re-irradiation can be a safe and effective treatment for recurrent GBM.

Re-irradiation fields should be highly conformal and target volumes minimized in an effort to reduce late side effects. A general guideline would be to keep volumes <4–5 cm and cumulative dose <100 Gy to prevent high rates of toxicity (43). Total dose and dose per fraction can be reduced as needed to compensate for an oversized re-treatment volume. The most commonly employed regimens are 35 Gy in 10 fractions and 24–36 Gy in 4–6 fractions.

The patient's PS and effect of re-irradiation on QOL should be weighed, as should the impact of a drawn out treatment course in the setting of poor prognosis.

Combination treatments and future directions

The inclusion of TMZ to re-irradiation has been well-studied and shown to be safe and effective with median survival ranging from 5.1 to 10.1 months after combination therapy (44-47). Darakchiev *et al.* placed Gliadel wafers in the resection cavity following surgical resection and I-125 seed implants in 34 patients with recurrent GBM. Median survival was 15.9 months, however, RN was observed in 24 % of cases when tumor volume was >30 cm^3 (29). Bevacizumab in combination with radiation retreatment has also been evaluated in a number of prospective studies. These studies have reported median survival ranging from 7.4 to 18 months with acceptable rates of toxicity (35,48-51). Of note, there are case reports of bevacizumab reversing radiation-induced necrosis and (52,53) in a small (n=14) randomized crossover study, all bevacizumab-treated patients (n=13 after crossover) developed improvement in neurologic signs and symptoms (54). The NRG 1205 trial randomizes patients to bevacizumab alone *vs.* HFSRT (35 Gy in 10 fractions) with bevacizumab (NCT02671981); it completed accrual in 2016, and we await the results. Given their success in preclinical glioma models and other solid tumors, immune modulators such as nivolumab, ipilimumab, and pembrolizumab are also being evaluated in combination with re-irradiation. Nivolumab and pembrolizumab are both PD-1 inhibitors and ipilimumab targets CTLA-4. The results of a phase I evaluation of combination nivolumab and ipilimumab in recurrent glioblastoma (CHECKMATE-143 trial) were recently updated at the American Society of Clinical Oncology 2016 annual meeting, showing that the combination is relatively safe with no treatment-related deaths. In addition, cohort 1 with nivolumab alone had no grade 3–5 toxicity, however the combination arms of nivolumab 1 mg/kg and ipilimumab 3 mg/kg had 9 (90%) of patients experienced grade 3–4 treatment related toxicity and 7 (70%) had serious treatment related toxicity. The combination of nivolumab 3 mg/kg and ipilimumab 1 mg/kg had 5 (25%) grade 3–4 toxicity with 2 (10%) serious treatment related toxicity. The 12 month OS was 40% for the nivolumab 3 mg/kg alone, 30% for the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg and 25% for the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (55). There are additional ongoing safety and efficacy immunotherapy studies, such as NRG-BN002, which introduces ipilimumab and nivolumab into maintenance TMZ therapy, or another study which combines HSFRT re-irradiation with pembrolizumab and bevacizumab (NCT02313272). Promising preclinical data has also shown that glioma cell growth can be inhibited through changes in diet. These effects are amplified with the addition of RT and together may increase longevity of life. More specifically, a ketogenic low-calorie diet is recommended and has been shown to be safe and feasible during primary chemoradiation and in the recurrent

setting. However, poor compliance related to palatability of such a diet could be a major drawback to implementation in the clinical setting. A less strict variant, high-fat, low-carbohydrate diet may be a more practical alternative with similar beneficial biological effects. Clinical trials assessing the integration of dietary manipulation with GBM re-irradiation are under way (NCT02149459, ERGO2-NCT01754350). Synergistic alternative therapies can only help in widening the window of application for re-irradiation in recurrent GBM, especially if/when the aforementioned novel combination therapies produce improved clinical outcomes.

Conclusions

There are myriad treatment options available to patients with recurrent glioblastoma, including repeat surgery, systemic therapy, and re-irradiation, or some combination thereof. Re-irradiation appears to be beneficial in a subgroup of patients. The data presented in this review shows re-irradiation to be safe in a well-selected group of patients, although there are certainly limitations in the available literature. The impact of re-irradiation on QOL is not well documented and will be an important component of future prospective studies. The combination of re-irradiation with novel systemic agents is a promising future direction in this patient population, which warrants prospective study in clinical trials.

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Footnote

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