Re-irradiation alternatives for recurrent high-grade glioma (Review)

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Abstract. Despite advances in the fields of surgery, chemotherapy and radiotherapy, the prognosis for high-grade glioma (HGG) remains unsatisfactory. The majority of HGG patients experience disease recurrence. To date, no standard treatments have been established for recurrent HGG. Repeat surgery and chemotherapy demonstrate moderate efficacy. As recurrent lesions are usually located within the previously irradiated field, a second course of irradiation was once considered controversial, as it was considered to exhibit unsatisfactory efficacy and radiation-related toxicities. However, an increasing number of studies have indicated that re-irradiation may present an efficacious treatment for recurrent HGG. Re-irradiation may be delivered via conventionally fractionated stereotactic radiotherapy, hypofractionated stereotactic radiation therapy, stereotactic radiosurgery and brachytherapy techniques. In the present review, the current literature regarding re-irradiation treatment for recurrent HGG is summarized with regard to survival outcome and side effects.

Contents

1. Introduction

In the United States, high-grade glioma (HGG) [World Health Organization (WHO) grade III-IV] (1) accounts for >60% of primary central nervous system tumor in adults, accounting for >60% of all brain tumors (2). Following the development of temozolomide (TMZ), which is administered concurrently or as an adjuvant after radiotherapy, the median survival time of glioblastoma patients has improved from 12.1 (no TMZ treatment) to 14.6 months (with TMZ treatment) (3). However, recurrence remains a problem in the majority of cases due to the infiltrative and radioresistant nature of the tumor cells (4). External beam re-irradiation in HGG was first reported in 1996 (5). However, severe toxicity was observed and post-overall survival (OS) (median OS after re-irradiation) and post-progression free survival (PFS) (median PFS after re-irradiation) times (2.8 and 1.4 months, respectively) were unsatisfactory (6-9). Following the development of irradiation techniques, re-irradiation may be delivered through conventionally fractionated stereotactic radiotherapy, hypofractionated stereotactic radiation therapy, stereotactic radiosurgery and brachytherapy. Re-irradiation has been demonstrated to exhibit moderate therapeutic efficacy with acceptable toxicities. Fokas *et al* (10) reported no significant difference between post-OS time following re-irradiation (9 months) and re-surgery (9 months) (P>0.05). Furthermore, a retrospective cohort study of 111 patients with recurrent glioblastoma multiforme compared survival between re-irradiation, resection and chemotherapy (11). The median survival after treatment was 37, 30 and 26 weeks, respectively, suggesting that re-irradiation serves as an effective salvage therapy. Furthermore, Archavlis *et al* (11) revealed that re-irradiation significantly improved survival time compared with re-operation and chemotherapy alone (11). Currently, re-irradiation alternatives for recurrent HGG vary among medical centers. Conventionally fractionated stereotactic radiotherapy is used for the majority of cases, as this technique causes the least damage to normal tissues (6,12). As a result of increased understanding with regard to radiation biology, hypofractionated stereotactic radiation therapy, which delivers a higher dose than conventionally fractionated stereotactic radiotherapy, may also be administered (13,14). Stereotactic radiosurgery, commonly used to deliver high doses in a single fraction, is particularly advantageous for the treatment of smaller lesions (15,16). In addition, brachytherapy, which is an invasive radiotherapy, presents an additional treatment

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method for recurrent HGG (17,18). Novel techniques such as pulsed reduced dose rate radiotherapy (19) and boron neutron capture therapy (20) have also been investigated. However, data regarding survival and treatment-related toxicities remain inconsistent (6,12-20). Thus, in the present review, an overview of the treatment alternatives for re-irradiation is provided with regard to survival outcomes and side effects.

2. Treatment alternatives for re-irradiation

Conventionally fractionated stereotactic radiotherapy (FSRT). FSRT is defined as radiotherapy delivered at a dose of <3 Gy per fraction, with the aim of minimizing normal tissue toxicity. A number of previous studies have reported the use of FSRT (Table I). In these studies, the post-OS time ranged between 8 and 16 months, and the post-PFS time ranged between 5 and 8 months (6,12,21-27). The highest post-OS time observed for WHO grade III glioma was 16 months (22,23). Regarding WHO grade IV glioma, when a second course of irradiation was combined with thermotherapy, the highest post-OS time was 13.4 months (24). Furthermore, Cho *et al* (21) reported that post-OS time was 12 months for individuals in a relatively poor condition [median Karnofsky performance status (KPS) score, 60] (28) who could not tolerate aggressive treatment, indicating that FSRT may present a useful treatment in this subset of patients. Bevacizumab, a humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF), is a feasible anti-angiogenic drug that is often used in the treatment of glioma (29). Compared with FSRT alone, FSRT in combination with bevacizumab significantly increases post-OS time (5.7 vs. 8.6 months, respectively) and post-PFS time (2.5 vs. 5.6 months, respectively) (27). In the present review, to compare the incidence of severe toxicity among previous studies, severe toxicity was defined as the following: The occurrence of ≥grade 3 adverse events according to each study, clinical or pathological radionecrosis, complications requiring surgery, and the occurrence of meningitis or wound infection.

Overall, the severe toxicity rate of FSRT ranged between 0 and 16%. In a study with a dose scheme of 41.6/2.66 Gy and the largest planning target volume reported to date, the side effects were well tolerated with a toxicity rate of 7.10% (26). No significant increase in toxicity was identified in patients receiving FSRT treatment combined with TMZ or bevacizumab.

FSRT treatment aims to minimize damage to normal tissues by fractionation, which is most beneficial in patients with large lesions or lesions adjacent to eloquent structures. Furthermore, the severe toxicity rate for FSRT was relatively low when compared with other re-irradiation alternatives, which are also discussed in this review.

Hypofractionated stereotactic radiotherapy (HSRT). HSRT, usually administered at a fractional dose of >3 Gy, takes advantage of a higher fractional dose of stereotactic radiosurgery (SRS), while maintaining the merits of FSRT in the protection of normal brain tissue. As shown in Table II, HSRT has been reported to be effective in recurrent HGG, with a post-OS time ranging from 7.4-16.5 months and a post-PFS time ranging from 5.8-15 months (7-10,13,14,30-38). It was demonstrated that patients treated with HSRT exhibited the same post-OS time of 9 months as patients treated with repeat surgery (P>0.05) (10). In a previous study by Patel *et al* (34), patients with smaller tumor volumes (median, 10.4 ml) were treated with SRS, whereas patients with larger tumor volumes (median, 51.1 ml) were treated with HSRT. The post-OS time for HSRT was 7.4 months compared with 8.5 months for SRS (P=0.81) (34). These results revealed that when indications were carefully considered, no significant differences in survival time were identified between patients treated with HSRT or re-operation and SRS. With regard to total dose of HSRT, Vordermark *et al* (13) reported that post-OS time was longer in patients administered a total dose of 30 Gy when compared with those treated with a total dose of <30 Gy (P=0.051). Fogh *et al* (35) observed that a total dose of ≥35 Gy resulted in an improved post-OS time. However, patients who received a dose of >40 Gy exhibited 6.4 times the risk of damage compared with those who received ≤ 40 Gy (30). Thus, a total dose of 30-35 Gy is the dose applied by the majority of radiation oncologists. A recent study of 147 patients treated with HSRT reported a post-OS time of 11 months for grade IV tumors (35), which is longer than that reported by Vordermark *et al* (13) and Patel *et al* (34). However, conservative dose may partially account for this survival difference, as one-third of patients only received 20 Gy in the study by Vordermark *et al* (13).

Another previous study indicated that TMZ may act as a radiation sensitizer (39). Thus, TMZ in combination with HSRT has also been investigated. Grosu *et al* (31) reported that HSRT treatment in combination with TMZ significantly increased survival time compared with HSRT treatment alone (11 vs. 6 months; P=0.04). However, controversy remains over whether TMZ or bevacizumab increase the efficacy of HSRT. Fogh *et al* (35) hypothesized that bevacizumab confers no survival advantage when combined with irradiation, however, only 4/147 patients received bevacizumab in this study. Using a treatment scheme modeled around the study by Voredermark *et al* (13), Gutin *et al* (33) investigated combined HSRT and bevacizumab treatment and found that survival time was longer in patients receiving combined treatment when compared with the results for HSRT alone from the study by Vordermark *et al* (13), particularly when larger tumor volumes were considered: Post-OS, 16.5 vs. 15.4 months (WHO grade III) and 12.5 vs. 7.9 months (WHO grade IV) (33).

Generally, combined treatment with HSRT and bevacizumab or TMZ has demonstrated an increased survival time of 12.2-16.5 months. In addition to bevacizumab, other inhibitors of the VEGF pathway, such as sorafenib and sunitinib, have been investigated for the treatment of recurrent HGG. In 2012, a phase I study of sorafenib combined with HSRT achieved a median post-OS time of 24 months, which is the longest post-OS time reported to date (40). In 2014, a pilot study of HSRT and sunitinib reported a post-OS time of 12.7 months, which is the longest post-OS time reported for recurrent glioblastoma multiforme (GBM) (38). However, further study is required to validate these results.

The severe toxicity rate for HSRT ranges between 0 and 60%. The highest toxicity rate was observed in a study by Voynov *et al* (7), however, this may have been due to the small sample size of only 10 patients. Although combined

Table I. Re-irradiation studies employing conventionally fractionated stereotactic radiation therapy.

First author, year	Patients, n	Median KPS	WHO grade (n)	TI[c], months	Total dose/ fractional dose, Gy	Post-OS time[d], months	Post-PFS time[d], months	PTV[c], ml	Prognostic factors	Rate of severe toxicity, %	(Ref.)
Cho *et al*, 1999	25	60 (40-80)	III (10) IV (15)	19	37.5/2.5	12	NR	74 (10-200)	WHO grade, age, KPS, tumor volume	16	(21)
Combs *et al*, 2005	53	≥80, 88%[b]	IV (53)	10	36/2	8	5	49 (7.5-632)	Resection at relapse	0	(6)
Combs *et al*, 2005	172	≥80 (III, 93%; IV, 63%)[b]	II (71) III (42) IV (59)	48, grade II 32, grade III 10, grade IV	36/2	16, grade III 8, grade IV	8, grade III 5, grade IV	49.3 (2.5-636)	WHO grade, TTP	0.60	(22)
Combs *et al*, 2005	40	≥80, 95%[b]	III (40)	31.5	36/2	16	8	56.2 (25.1-296.2)	None	0	(12)
Combs *et al*, 2008	25	≥70, 92%[b]	II (7) III (10) IV (8)	36	36/2 + TMZ	8 (OS-6, 81%; OS-12, 25%)	5	50 (16-149)	None	0	(23)
Maier-Hauff *et al*, 2011	59	90 (60-100)	IV (59)	NR	30/2 + thermotherapy	13.4	NR	46.5 (6.6-108.0)	Tumor volume	6.8-15.3	(24)
Minniti *et al*, 2011	36	70 (60-100)	IV (59)	14	37.5/2.5 + TMZ	9.7 (OS-6, 84%; OS-12, 33%)	5 (PFS-6, 42%; PFS-12, 8%)	32.1 (12.3-72.4)	KPS, treatment interval, MGMT methylation	11	(25)
Hundsberger *et al*, 2013	14	70 (60-90)	III (6) IV (8)	40.9 (6.1-387.9)	41.6/2.66	9	5.1	190 (47-373)	Prior therapies, tumor volume	7.10	(26)
Flieger *et al*, 2014	71	80 (40-100)	III (19) IV (52)	≥6	36/2 + Beva	8.6 5.7 (non-Beva)	5.6 (PFS-6, 42.1%)	34.88[a] (1.95-157.94) (non-Beva 2.5)	Beva, chemotherapy re-irradiation dose, GTV	7.20	(27)

[a]GTV; [b]these studies only provided the percentage of patients within a specific KPS range; [c]data presented as the median (range); [d]data presented as the median. KPS, Karnofsky performance status; WHO, World Health Organization; OS, overall survival; PFS, progression-free survival; Ti, treatment interval (interval between initial radiotherapy and re-irradiation); post-OS, median OS time after re-irradiation; post-PFS, median PFS time after re-irradiation; OS-6, 6-month OS rate ; OS-12, 12-month OS rate; PFS-6, 6-month PFS rate; PFS-12, 12-month PFS rate; PTV, planning target volume; NR, data not reported; TMZ, temozolomide; MGMT, O6-methylguanine-DNA methyltransferase; Beva, bevacizumab; GTV, gross target volume; TTP, time to progression.

Table II. Re-irradiation studies employing hypofractionated stereotactic radiotherapy.

First author, year	Patients, n	KPS[a]	WHO grade (n)	TI[a], months	Total/fractional dose, Gy	Post-OS time, months	Post-PFS time, months	PTV[a], ml	Prognostic factors	Rate of severe toxicity, %	(Ref.)
Shepherd *et al*, 1997	33	80 (60-100)	NR	29 (5-174)	35/5	11	NR	24[b]	Grade	18.2	(30)
Voynov *et al*, 2002	10	80 (60-100)	NR	19	30/5	10.1 (OS-12, 50%; OS-24, 33.3%)	NR	34.69[b] (4.29-75.23)	NR	60	(7)
Vordermark *et al*, 2005	19	90 (60-90)	III (5) IV (14)	19 (3-116)	30/5	9.3 (15.4, grade III; 7.9, grade IV)	4.9 (TTP)	15 (4-70)	NR	0	(13)
Grosu *et al*, 2005	44	80 (40-100)	III (10) IV (34)	16	30/5	8	NR	15[c] (1-61)	Interval, TMZ	7	(31)
Ernst-Stecken *et al*, 2007	15	80 (60-100)	III (4) IV (11)	10 (2-47)	35/7	12 (OS-12, 43%; OS-18, 28%)	15 (PFS-6, 75%; PFS-12, 53%)	22.4 (4.22-86.79)	GTV, PTV, initial grade	NR	(32)
Gutin *et al*, 2009	25	90 (70-100)	III (5) IV (20)	15	30/6 + Beva	16.5, grade III 12.5, grade IV	7.5, grade III 7.3, grade IV	34 (2-62)	NR	12	(33)
Patel *et al*, 2009	10	90 (70-90)	IV (10)	14.9	36/6	7.4	NR	51.1[b] (16.1-123.3)	Tumor response	10	(34)
Henke *et al*, 2009	31	90 (60-100)	III (2) IV (29)	18 (3-109)	20/5	10.2	NR	55 (0.9-277)	Age, KPS, interval, surgery after HSRT	0	(14)
Fokas *et al*, 2009	53	70	IV (53)	12	30/3	9	PFS-12 22% PFS-24 5%	35.01 (3-204)	KPS	0	(10)
Fogh *et al*, 2010	147	≥60	III (42) IV (105)	8	35/3.5	10, grade III 11, grade IV	NR	22[c] (0.6-164)	Age, GTV, treatment interval	1	(35)
Kim *et al*, 2011	8	65	III (3) IV (5)	NR	25/5	7.6 (4.2-16.2)	NR	69.5	NR	12.5	(8)
Minniti *et al*, 2013	54	80 (60-100)	III (16) IV (38)	15.5	30/6 + TMZ	12.4 (OS-12, 53%)	6 (OS-12, 24%; OS-24, 16%)	30.3 (12.3-53.4) OS-24 10%)	KPS, grade	35-42	(36)
Shapiro *et al*, 2013	24	80 (70-100)	III (4) IV (20)	NR	30/6 + Beva	14.0, grade III 12.2, grade IV	7.5 11.1, grade III 6.8, grade IV	35 (3-62)	Tumor response	0	(37)
McKenzie *et al*, 2013	35	80 (50-100)	III (3) IV (32)	14.2 (3.6-83.1)	30/5f	8.6 (OS-6, 66%; OS-12, 34%; OS-24, 3%)	NR	8.54 (0.4-46.56)	Gender, local control at 6 months,	26-35	(9)
Wuthrick *et al*, 2014	11	WHO PS, 0-2	III (3) IV (8)	19.5	30-42/2.5-3.5 + sunitinib	11 (12.7 for GBM)	5.8 (6.4 for GBM) (PFS-6, 45%; PFS-6, 50% for GBM)	16.75[b] (0.05-72.01)	Tumor response at the 2-month MRI	9	(38)

[a]Data presented as the median (range); [b]tumor volume; [c]GTV. KPS, Karnofsky performance status; WHO, World Health Organization; OS, overall survival; PFS, progression-free survival; TD, total dose; TI, treatment interval (interval between initial radiotherapy and re-irradiation); FD, fractional dose; post-OS, median OS time after re-irradiation; post-PFS, median PFS time after re-irradiation; OS-6, 6-month OS rate; OS-12, 12-month OS rate; OS-24, 24-month OS rate; PFS-6, 6-month PFS rate; PFS-12, 12-month PFS rate; PFS-24, 24-month PFS rate; PTV, planning target volume; GTV, gross target volume; NR, data not reported; MRI, magnetic resonance imaging; PS, performance status; TMZ, temozolomide; Beva, bevacizumab.

Table III. Re-irradiation studies employing SRS.

First author, year	Patients, n	KPS[a]	WHO grade (n)	TI[a], months	Total/fractional dose, Gy	Post-OS time, months	Post-PFS time, months	PTV[a], ml	Prognostic factors	Rate of severe toxicity, %	(Ref.)
Hall *et al*, 1995	35	70 (50-90)	III (9) IV (26)	NR	20/1	8	NR	21-30	KPS, age	20	(42)
Cho *et al*, 1999	46	70 (50-90)	III (29) IV (42)	10	17/1	11 (OS-12, 42%)	NR	30 (3-125)	WHO grade, age, KPS, tumor volume	14-24	(21)
Combs *et al*, 2005	32	80 (70-100)	IV (32)	10	15/1	10 (OS-6, 72%; OS-12, 38%)	5 (PFS-6, 33%)	10 (1.2-59.2)	None	0	(43)
Patel *et al*, 2009	26	80 (50-100)	IV (26)	12.5	18/1	8.5	NR	10.4 (0.3-60.1)	NR	7.7	(34)
Maranzano *et al*, 2011	13	90 (70-100)	IV (13)	9	17/1	11 (OS-6, 77%; OS-12, 36%)	NR	5.3[b] (0.6-14)	None	23.1	(44)
Torok *et al*, 2011	14	NR	IV (14)	NR	27/3	10 (OS-6, 79%; OS-12, 30%)	5 (TTP)	6.97[c]	NR	0	(45)
Elliott *et al*, 2011	26	90 (70-100)	III (10) IV (16)	NR	15/1	13.5 (12 for GBM; OS-12, 37%) (26.4 for AA; OS-12, 80%) (9.7 for AMOA; OS-12, 20%)	5.5	1.22	Age at HGG diagnosis, age at GKR for recurrence, interval between surgery and recurrence, KPS, RPA class, tumor volume, RD	7.7	(15)
Cuneo *et al*, 2012	63	80 (50-90)	III (14) IV (49)	20	15/1 + Beva	10	6	4.8	Beva, KPS, age	8-14	(16)
Conti *et al*, 2012	12	NR	IV (12)	NR	20/2	12 vs. 7 (SRS/TMZ vs. SRS)	7 vs. 4 (PFS-6, 66.7 vs. 18%)	13.8	TMZ	41.7	(46)
Skeie *et al*, 2012	51	76	IV (51)	NR	12.2	12	6 (TTP)	12.4[b]	Treatment group, eloquent brain structures, tumor volume, further intervention after retreatment, RPA, neurological deficits, time to recurrence, adjuvant therapy, tumor location	9.8	(47)
Cabrera *et al*, 2013	15	90 (80-100)	III (7) IV (8)	NR	24 or 18/1, <3-cm lesions 25/5, 3-5 cm lesions	14.4	3.9 (PFS-6, 20%)	NR	NR	6.7	(48)
Martínez-Carrillo *et al*, 2014	87	83	NR	13.8 (4-61)	18/1-3	10 (17 for AA; 7.5 for GBM)	NR	8.7[b] (1-42.6)	Age, tumor and treatment volume at recurrence, RPA, KPS, histology, margin to the PTV	0	(49)

[a]Data presented as the median (range); [b]tumor volume; [c]GTV. SRS, stereotactic radiosurgery; KPS, Karnofsky performance status; WHO, World Health Organization; TI, treatment interval (interval between initial radiotherapy and re-irradiation); TD, total dose; FD, fractional dose; OS, overall survival; PFS, progression-free survival; post-OS, median OS time after re-irradiation; post-PFS, median PFS time after re-irradiation; OS-6, 6-month OS rate; OS-12, 12-month OS rate; OS-24, 24-month OS rate; PFS-6, 6-month PFS rate; PFS-12, 12-month PFS rate; PFS-24, 24-month PFS rate; TTP, time to progression; PTV, planning target volume; GTV, gross target volume; RPA, recursive partitioning analyse; RD, radiosurgical dose; NR, data not reported; GKR, Gamma Knife radiosurgery; TMZ, temozolomide; Beva, bevacizumab; GBM, glioblastoma multiforme; AA, anaplastic astrocytoma; AMOA, anaplastic mixed oligoastrocytoma; HGG, high-grade glioma.

treatment with HSRT and TMZ increased the severe toxicity rate to 35-42%, grade 3 neurological deterioration attributable to radiation-induced necrosis was managed successfully with high-dose dexamethasone and/or surgery (36). In contrast to TMZ, bevacizumab combined with HSRT achieved a relatively low toxicity rate of 0-12% (33,37). We hypothesize that the anti-angiogenic properties of bevacizumab may protect against the potential toxicity of dose escalation.

Although the severe toxicity rate for HSRT is higher than that of FSRT, HSRT remains well tolerated and fewer treatment fractions are required, reducing overall treatment time, which is particularly important for terminally ill patients. Notably, in the literature, HSRT combined with bevacizumab resulted in less toxicity when compared with HSRT combined with TMZ.

SRS. SRS is usually performed for relatively small lesions (maximal diameter, <4 cm) as high doses may be delivered in a single fraction with a lower incidence of treatment-associated morbidity (41). As shown in Table III, previous studies have demonstrated that SRS is beneficial for the management of recurrent glioma. Patients treated with SRS exhibited post-OS times ranging from 7-14.4 months, post-PFS times ranging from 3.9-6 months and a median time-to-progression (TTP) ranging from 4-6 months (12,15,16,34,42-49). In a previous study by Skeie *et al* (47), a total of 32 patients underwent SRS, 26 patients underwent repeat surgery and 19 patients were treated with both procedures. The results revealed that when compared with patients undergoing repeat surgery, the patients treated with SRS demonstrated an increased post-OS time (6 vs. 12 months; P=0.001) and an increased post-TTP time (2 vs. 6 months; P=0.009) (47). A higher rate of late complications was also previously observed in patients treated with SRS compared with FSRT (30 vs. 8%; P<0.05), however, no difference in survival time was identified between the treatments (12). The longest survival time of 14.4 months was reported by Cabrera *et al* (48). In this study, 50% of patients exhibited grade III tumors and received combined SRS and bevacizumab treatment, which may account for this result (48). To assess the efficacy of SRS and adjuvant bevacizumab, Cuneo *et al* (16) enrolled 63 patients and reported that for recurrent grade IV HGG patients, SRS combined with bevacizumab significantly increased the post-OS time (11.2 vs. 3.9 months), post-PFS time (5.2 vs. 2.1 months) and the 12-month survival rate (50 vs. 22%) when compared with SRS treatment alone (16). Similar findings were reported in the study by Conti *et al* (46), which demonstrated that the median survival time for patients undergoing SRS/TMZ was longer than that for those treated with SRS alone (12 vs. 7 months; P<0.01). Elliott *et al* (15) reported post-OS times of 12.9, 26.4 and 9.7 months for GBM, anaplastic astrocytoma and anaplastic mixed oligoastrocytoma patients, respectively, which were longer than the post-OS times exhibited by patients treated with FSRT or HSRT. However, the median lesion volume in this study was 1.22 ml, indicating that SRS may only benefit patients exhibiting smaller tumor volumes.

Overall, the severe toxicity rate for SRS ranges between 0 and 41.7%. Following a literature review, Mayer and Sminia (50) concluded that radiation-induced normal brain tissue necrosis occurs at a biologically effective dose of >200 Gy and a normalized total dose ($NTD_{cumulative}$) of >100 Gy (50). This conclusion may explain the severe toxicity rate of 23% reported in the study by Maranzano *et al* (44), in which 3 patients who exhibited brain radionecrosis were all treated with a $NTD_{cumulative}$ dose of >120 Gy. Notably, the highest toxicity rates were associated with TMZ (46). By contrast, bevacizumab combined with SRS has been shown to result in fewer complications, with a severe toxicity rate ranging between 6.7 and 14% (16,48).

The aforementioned studies indicate that SRS is beneficial for certain individuals with focal and small lesions. In comparison with HSRT, SRS treatment combined with bevacizumab resulted in less adverse reactions when compared with TMZ. The results also indicate that $NTD_{cumulative}$ doses should not exceed 100 Gy, to prevent radionecrosis.

Brachytherapy (BT). BT is an invasive form of radiotherapy in which radioactive seeds containing radioisotopes, such as iodine-125 (^{125}I) and iridium-192 (^{192}Ir), are placed in tumor sites, permanently or temporarily, during surgery (51). The radioisotope emits γ-rays that suppress tumor cells (51). The major advantage of BT is that it allows the delivery of a higher dose of radiation to the tumor volume, however, infection and hemorrhage are common (51). As shown in Table IV, the post-OS time following BT ranges between 32 and 71.6 weeks, and PFS ranges between 23.6 and 32 weeks (11,17,18,52-58). Archavlis *et al* (11) reported that BT treatment resulted in significantly longer survival times (37 weeks) when compared with re-resection (30 weeks) or TMZ (26 weeks) alone, with less complications (11). Due to differences in total dose, dose rate, methods of placement and source activity, it is difficult to compare survival data directly among various studies. A number of studies have attempted to establish the appropriate total dose for BT. Regarding a low dose rate, Chan *et al* (54) found that patients who received doses of <50 Gy, >50 Gy and <60 Gy, or >60 Gy exhibited no significant differences in survival after retreatment. Regarding a high dose rate, Tselis *et al* (56) treated 84 patients with computed tomography-guided interstitial ^{192}Ir high dose rate BT for recurrent cerebral GBM. The results demonstrated that patients who received total doses of 30, 40 or 50 Gy exhibited no significant differences in post-OS times. Thus, these results suggest that total dose does not affect survival time after re-irradiation. According to the literature, recurrent GBM patients treated with high and low dose rate radiotherapy experienced survival times of 32-37 and 32-69 weeks, respectively. These results indicate that low dose rate radiotherapy results in increased survival times when compared with high dose rate radiotherapy, which could possibly be attributed to the low dose rate characteristic of synchronizing tumor cells to the radiosensitive G_2-M phase (59). However, the optimal dose rate remains controversial. Koot *et al* (60) investigated BT treatment at various dose rates in patients with primary glioblastoma and concluded that dose rate did not affect survival time. In another study, BT treatment combined with carmustine wafers for the treatment of recurrent GBM resulted in the longest survival time of 69 weeks; however, the rate of severe toxicity was 35.3% (18). Despite a severe toxicity rate of 35% in 17 patients, Archavlis *et al* (61) reported only a single case of radionecrosis in a patient with a relatively large tumor volume of 38.1 ml (61). The study attributed the one case of radionecrosis to the

Table IV. Re-irradiation studies employing brachytherapy.

First author, year	Patients, n	KPS[a]	WHO grade (n)	Treatment type	Source activity[a], mCi	Total dose[a], Gy	Dose rate[a], cGy/h	Post-OS time, weeks	Post-PFS time, weeks	PTV[a], ml	Prognostic factor	Rate of severe toxicity, %	(Ref.)
Simon *et al*, 2002	42	80 (50-100)	IV (42)	Temp + LDR + ^{192}Ir implant	NR	50 (15-60)	37 (16-73)	50 (8-207)	NR	23 (1.6-122)	KPS, pre-implant volume	24-33.3	(51)
Tatter *et al*, 2003	21	80 (60-100)	IV (15) III (6)	Temp + LDR + ^{125}I GliaSite	73-459	40-60	41-61	12.7 months (17.9 months for non-GBM; 8 months for GBM)	NR	NR	NR	19.0	(53)
Larson *et al*, 2004	38	90 (60-100)	IV (38)	Perm + LDR + ^{125}I implant	0.67 (0.40-0.93)	300 (150-500)	15 (7-24)	52	16	21 (1-68)	KPS, age, tumor volume	10.5	(17)
Chan *et al*, 2005	24	80 (50-100)	IV (24)	Temp + LDR + ^{125}I GliaSite	NR	53.1 (29.9-80)	52.7	9.1 months (1.3-23.6 months)	NR	≤30	KPS	8	(54)
Gabayan *et al*, 2006	95	80 (40-100)	GBM (80) non-GBM (15)	Temp + LDR + GliaSite	369 (90-950)	60 (38-72.5)	52.3	36.3 (OS-12, 31.1%) (35.9 for GBM; 43.6 for non-GBM)	18.7 (TTP)	NR	KPS	2.1	(55)
Tselis *et al*, 2007	84	80 (50-100)	IV (84)	Temp + HDR + ^{192}Ir implant	NR	40 (30-50)	5.0 Gy twice a day	37	NR	51 (3-207)		3.6	(56)
Darakchiev *et al*, 2008	34	80 (60-100)	IV (34)	Perm + LDR + ^{125}I implant + BCNU wafers	0.67/seed	120	NR	69 (OS-6, 82%; OS-12, 66%)	47 (PFS-12, 32%)	34 (8-90)	KPS, Iseed activity, age	35.3	(18)
Fabrini *et al*, 2009	21	80	III (3) IV (18)	Temp + HDR + ^{192}Ir balloon-shaped applicator	219 GBq (106-323)	18	6171.4[b]	8 months (4.0-18.5 months)	(PFS-6, 42%) NR	13.8 (9.7-19.8)	KPS	9.5	(57)
Archavlis *et al*, 2013	50	90	IV (50)	Temp + HDR + ^{192}Ir implant	NR	40 (30-50)	5.0 Gy twice a day	37	32 (PFS-6, 64%)	46 (3-207)	TTP1, TTP2	10	(11)
Kickingereder *et al*, 2014	98	90 (60-100)	IV (98)	LDR + ^{125}I implant	16.1 (2.1-63.3)	60	7.53	10.4 months (OS-3, 95.8%; OS-6, 85.2%; OS-12, 39.0%)	5.9 months (PFS-3, 77.6%; PFS-6, 48.8%; PFS-12, 16.2%)	17.4 (1.6-70.0)	KPS, age, adjuvant chemotherapy	NR	(58)
Archavlis *et al*, 2014	17	90 (80-100)	IV (17)	Temp + HDR + ^{192}Ir implant	NR	40	5.0 Gy twice a day	8 months	7 months	38.1	NR	35	(61)

[a]Data presented as the median (range); [b]calculated from information provided. KPS, Karnofsky performance status; WHO, World Health Organization; OS, overall survival; PFS, progression-free survival; post-OS, median OS after re-irradiation; post-PFS, median PFS after re-irradiation; OS-6, 6-month OS rates; OS-12, 12-month OS rate; OS-24, 24-month OS rate; PFS-6, 6-month PFS rate; PFS-12, 12-month PFS rate; PFS-24, 24-month PFS rate; TTP1, time to progression after initial irradiation; TTP2, time to progression after re-irradiation; RPA, recursive partitioning analysis; NR, data not reported; ; BCNU, carmustine; GBM, glioblastoma multiforme; perm, permanent; temp, temporary; LDR, low-dose rate; HDR, high-dose rate; I, iodium; Ir, iridium.

requirement for better fixation of the radioactive seeds, which would limit the radioisotopes from migrating. Discrete seed implants produce an inhomogeneous distribution of radiation dose, which is associated with radiation necrosis. This rationale also accounted for the lack of toxicity greater or equal to grade 3 in another study with a tumor volume of 46 ml (11). Treatment using GliaSite BT (Gliasite, Cytic Surgical Products, Palo Alto, CA, USA), a single spherical source of low dose rate radiation, may achieve lower toxicity (54,55). This technique utilizes an inflatable balloon that fits the resection cavity, contributing to a more uniform dose. KPS is the most common prognostic factor used in the literature, possibly due to the invasiveness of BT. Chan *et al* (54) reported that the median survival times for patients with KPS scores of >70 and <70 were 9.3 and 3.1 months, respectively. Furthermore, Gabayan *et al* (55) demonstrated that the median survival time was 45.3 weeks for patients with a KPS score of ≥90 compared with 34.9 weeks for patients with a KPS score <90.

Overall, BT may present a promising treatment, particularly in individuals in a better condition (i.e., with a higher KPS score). The use of TMZ and bevacizumab in combination with BT has not been investigated, however, combined carmustine and BT treatment has been shown to result in severe toxicity. Improved methods of seed fixation may prevent radionecrosis, while total dose and dose rate remain controversial. Further study is required to investigate these factors.

Novel techniques. Pulsed reduced dose rate radiotherapy (PRDR) employs a dose rate of 6 cGy/min, which allows for increased normal tissue repair. The technique was first reported by Cannon *et al* (19) in 2007 for the treatment of GBM. The total dose delivered to the tumor bed by PRDR was 104 Gy, and no radionecrosis was identified. Notably, the patient exhibited a radiographic response and clinical improvement. Adkison *et al* (62) conducted a study using a larger patient cohort, which included 103 patients with recurrent HGG. The median PRDR retreatment dose was 50 Gy, delivered in 1.8 to 2.0-Gy fractions at a dose rate of 0.0667 Gy/min. The post-OS times were 5.6 and 5.1 months for grade III and IV tumors, respectively. PRDR with cumulative doses of >100 Gy were also well tolerated. Notably, the mean treatment volume was 403.5±189.4 cm^3, which is the largest volume reported to date. In the study, only 16% of patients were treated with PRDR at first relapse, indicating its potential use as a first-line salvage treatment. Brain autopsy revealed evident necrosis in 26.7% (4/15) patients (62).

Boron neutron capture therapy (BNCT) utilizes boron-10-containing compounds, which selectively accumulate in tumor cells. When non-radioactive boron is irradiated with high energy neutrons, high-energy α particles and lithium nuclei are emitted, which leads to tumor cell death (63). This process possibly occurs via cell cycle arrest and apoptosis (64). Miyatake *et al* (65) investigated 22 cases of recurrent malignant glioma treated using BNCT. The results revealed that the post-OS time for all patients was 10.8 and 9.6 months for patients with glioblastoma. Pellettieri *et al* (20) reported a post-OS time of 8.7 months and a post-PFS time of 6 months in 12 recurrent cases of GBM, without the occurrence of severe acute toxicity. BNCT with bevacizumab was also found to benefit the survival of 4 recurrent HGG patients (66). BNCT selectively delivers a high radiation dose to the tumor, while limiting the toxicity to the surrounding normal tissues; this is a major advantage of the technique. In the future, further study is required to validate the role of BNCT in the treatment of recurrent high-grade glioma.

TM-601 is a synthetic peptide that binds to phosphatidyl inositide, a phosphorylated lipid on tumor cells (67). When TM-601 is labeled with ^{131}I, it may suppress tumor growth. Mamelak *et al* (68) investigated the efficacy and safety of ^{131}I-TM-601 (labeled with 10 mCi of ^{131}I) for use in recurrent HGG patients who had previously received irradiation treatment. The post-OS times were was 25.7, 77.6 and 23.6 weeks for doses of 0.25, 0.50 and 1.00 mg, respectively. No grade 3 or 4 toxicities were reported. This alternative treatment may be delivered easily via venous injection. However, the study by Mamelak *et al* (68) was a phase I study, and thus, phase II studies are required.

3. Conclusion

A number of invasive and non-invasive re-irradiation techniques with proven efficacy are available for the treatment of recurrent HGG. Certain factors, including proximity to sensitive risk structures, KPS and tumor volume, must be considered comprehensively to improve individualized radiotherapy. If the tumor is large or located close to eloquent structures, FSRT should be selected to limit damage to the vital organs. For terminally ill patients, HFSRT may reduce treatment time, subsequently improving quality of life. With regard to smaller and unifocal tumors, SRS may be used for the precise delivery of high doses of radiation. For the application of BT, which is an invasive treatment, the KPS score should be considered and the refinement of treatment protocols may improve survival time. Furthermore, adjuvant treatment with agents such as bevacizumab and TMZ may increase treatment efficacy. In addition, novel treatment modalities have exhibited promising results. For example, PRDR presents a potential modality for patients with relatively large tumors. Furthermore, BNCT may selectively deliver radiation doses and ^{131}I-TM-601 may also deliver radiation that is highly localized to tumor sites. When indications are considered carefully, certain patient subgroups may benefit from re-irradiation for the treatment of recurrent HGG. However, curative treatments remain to be identified and thus, further study is urgently required.

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