

Re-irradiation for recurrent high-grade gliomas: a systematic review and analysis of treatment technique with respect to survival and risk of radionecrosis

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Abstract

Background: Re-irradiation may be considered for select patients with recurrent high-grade glioma. Treatment techniques include conformal radiotherapy employing conventional fractionation, hypofractionated stereotactic radiotherapy (FSRT), and single-fraction stereotactic radiosurgery (SRS).

Methods: A pooled, population-weighted, multiple linear regression analysis of publications from 1992 to 2016 was performed to evaluate the relationships between re-irradiation technique and median overall survival (OS) and radionecrosis outcomes.

Results: Seventy published articles were analyzed, yielding a total of 3302 patients. Across all studies, initial treatment was external beam radiotherapy to a median dose of 60 Gy in 30 fractions, with or without concurrent chemotherapy. On multivariate analysis, there was a significant correlation between OS and radiotherapy technique after adjusting for age, re-irradiation biologically equivalent dose (EQD2), interval between initial and repeat radiotherapy, and treatment volume ($P < .0001$). Adjusted mean OS was 12.2 months (95% CI, 11.8–12.5) after SRS, 10.1 months (95% CI, 9.7–10.5) after FSRT, and 8.9 months (95% CI, 8.4–9.4) after conventional fractionation. There was also a significant association between radionecrosis and treatment technique after adjusting for age, re-irradiation EQD2, interval, and volume ($P < .0001$). Radionecrosis rate was 7.1% (95% CI, 6.6–7.7) after FSRT, 6.1% (95% CI, 5.6–6.6) after SRS, and 1.1% (95% CI, 0.5–1.7) after conventional fractionation.

Conclusions: The published literature suggests that OS is highest after re-irradiation using SRS, followed by FSRT and conventionally fractionated radiotherapy. Whether this represents superiority of the treatment technique or an uncontrolled selection bias is uncertain. The risk of radionecrosis was low for all modalities overall. Re-irradiation is a feasible option in appropriately selected patients.

Key words

glioma | radiosurgery | recurrent | re-irradiation | stereotactic radiotherapy

High-grade gliomas are World Health Organization (WHO) grade III and IV tumors and are the most common malignant primary central nervous system tumor in adults.¹ Current standard treatment is maximal safe surgical resection followed by external beam radiotherapy of 59.4 to 60 Gy in 30 to 33 fractions with concurrent and/or adjuvant chemotherapy, depending on histology and molecular

status.^{2–6} Despite advances in understanding the biological and molecular basis of disease, prognosis remains generally poor. For glioblastoma (grade IV), median survival is 14.6 months and 26.5% of patients are alive at 2 years. Local failure remains the most common mode of recurrence with 90% of tumors recurring within the initial site of disease.⁷

At recurrence, high-quality data to inform management are lacking.¹ Management options include repeat surgery, re-irradiation, cytotoxic chemotherapy, targeted agents, or best supportive care.⁸ For patients suitable for further treatment, median survival following first recurrence is approximately 6 to 12 months in patients receiving second-line systemic therapy with or without repeat surgery,^{9,10} and less than 12 months for patients receiving re-irradiation.^{11,12}

The most appropriate patients with recurrent high-grade glioma suitable for re-irradiation have been suggested to be those at least 6 months from initial treatment, with a Karnofsky Performance Status score greater than 60 and lesion diameter less than 40 mm.¹³ A review of the re-irradiation tolerance of the brain reports a low rate of radionecrosis following cumulative doses up to 100 Gy, and smaller volumes may be treated to higher doses without significantly greater risk.¹⁴ A number of additional re-irradiation studies have been published since this review and a range of radiotherapy techniques have been employed including conformal or intensity-modulated radiotherapy using conventional fractionation (1.8 to 2 Gy per fraction), hypofractionated stereotactic radiotherapy (FSRT), and single-fraction stereotactic radiosurgery (SRS).¹ Whether outcomes vary significantly according to dose, dose per fraction, or radiotherapy technique is not known.

We aimed to update the current literature on outcomes after re-irradiation for recurrent high-grade glioma and perform a pooled statistical analysis of published studies to assess differences in survival and rate of radionecrosis according to radiotherapy technique.

Methods

A systematic review was performed to identify relevant articles published in all languages in peer-reviewed journals between January 1, 1980 and December 31, 2016. Studies were eligible for inclusion if they reported outcomes in patients aged at least 18 years who received re-irradiation for recurrent WHO Grade III or IV glioma after having previously received conventionally fractionated radiotherapy. Studies employing re-irradiation techniques other than conventional radiotherapy, FSRT, or SRS (Gamma Knife[®] and linear accelerator-based)—such as brachytherapy or particle therapy—were excluded. Studies in which patients received re-irradiation in combination with repeat surgery and/or systemic therapies were not excluded because these patients were incorporated to varying degrees in the majority of studies. In the event of repeat publications or data arising from the same cohort more than once, efforts were made to use only the most recent for analysis. Publications with less than 20 patients or for which the full text was not available for review were excluded for statistical robustness. Conference abstracts, traditional reviews, editorials, and letters to the editor were also excluded.

MEDLINE, PubMed, and the Cochrane Database of Systematic Reviews databases were searched using relevant MeSH and non-MESH terms. The PubMed and Cochrane search strategy utilized “glioma,” “high-grade

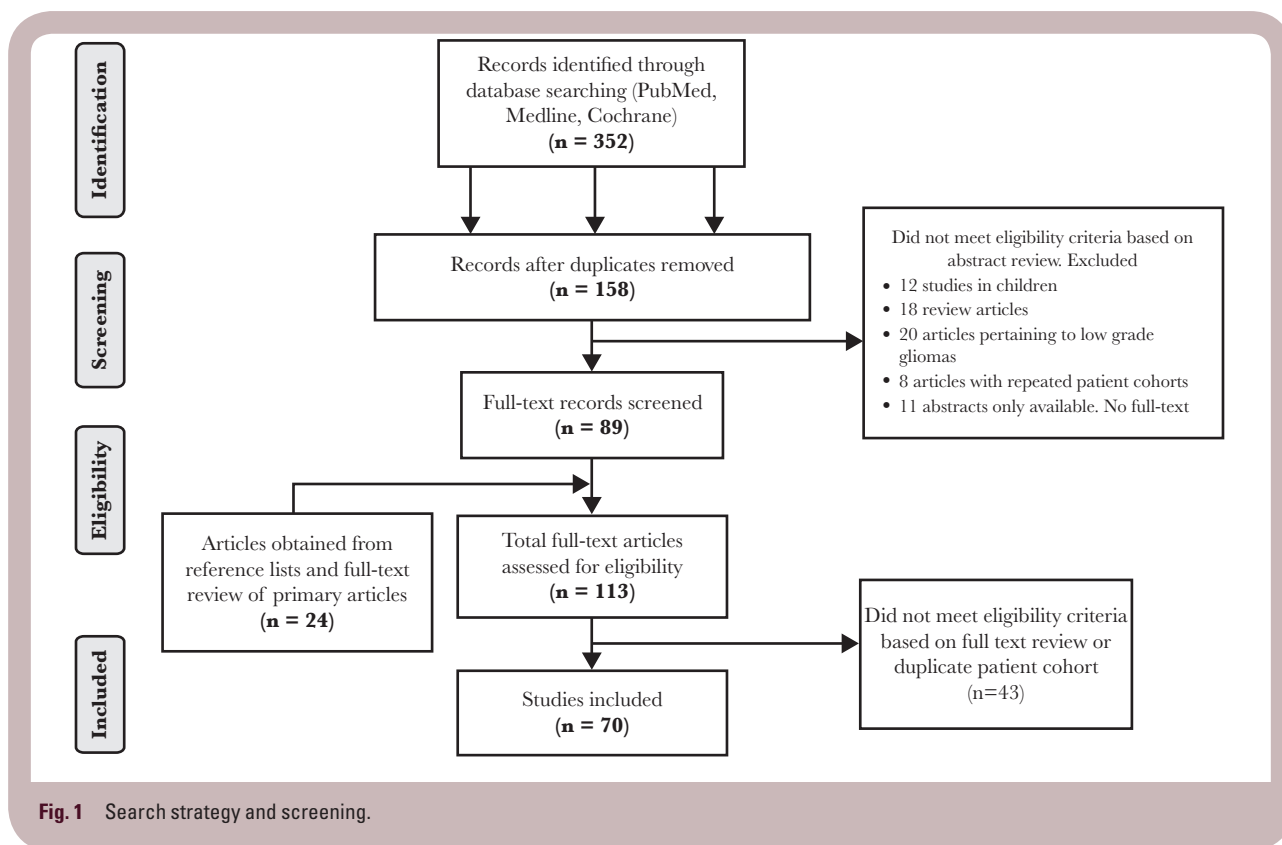
glioma,” “high grade glioma,” “recurrent,” “reirradiation,” “re-irradiation,” “radiotherapy,” “radiosurgery,” “Gamma Knife,” and “Cyber Knife.” The MEDLINE search strategy utilized algorithm terms “Glio*.tw” AND “Re-irrad*.tw” OR “reirrad*.tw” to source relevant articles. Results were screened initially using the title and abstract according to the inclusion and exclusion criteria. A secondary screen was then performed reviewing the full text of remaining articles and reference lists for additional potentially relevant articles.

Median overall survival (OS) and rate of radionecrosis were extracted from each study along with additional relevant clinical and technical information. Re-irradiation and total combined dose was calculated using the linear-quadratic model taking an $\alpha/\beta = 2$ to determine an equivalent total dose in 2-Gy fractions (EQD2). A formal meta-analysis methodology was not employed because included studies were not comparative.¹⁵ A population-weighted linear regression analysis was performed to evaluate the relationships between OS and radionecrosis rate (primary outcome variables) and radiotherapy modality, median age, median interval between radiotherapy treatments, total cumulative EQD2, re-irradiation EQD2, median dose per fraction, and median planning target volume (PTV) (explanatory variables). Treatment modality was the primary explanatory variable of interest and was divided into 3 groups: conventionally fractionated radiotherapy (Group 1), SRS (Group 2), and FSRT (Group 3). All statistical analyses were performed using Statistical Analysis System (SAS) software (SAS Version 3.4, SAS Institute Inc., Cary, NC, USA). Univariate analyses were performed using a one-way analysis of variance (ANOVA) or Kruskal-Wallis test. Pairwise comparison of variables was performed using Tukey’s post-hoc test. A multiple linear regression analysis weighted by study size was performed incorporating the explanatory variables (treatment modality, age, interval, and PTV). Independent analyses for total cumulative EQD2, re-irradiation EQD2, and re-irradiation dose per fraction were performed to create 3 multivariate models each for OS and radionecrosis. A statistical significance of $P < .05$ was used for all analyses.

Explanatory variables that did not reach statistical significance were removed unless they were confounders of the primary relationship between treatment modality type and outcome. Valid confounders were defined as explanatory variables in the multivariate analysis whose exclusion changed the measure of effect of modality type on the outcome of interest by more than 10%. These were tested independently and variables that were not valid confounders and not statistically significant were excluded from the multivariate model. Studies with missing data were excluded from individual models as appropriate. Coefficients of multiple determination or R-squared values were assessed to determine the percentage of variability accounted for by explanatory variables.

Results

Initially 352 publications were identified. After screening, 70 were included, yielding 3302 patients (Figure 1



and Table 1). Patients initially received external beam radiotherapy to a dose of 48.3 to 60 Gy (median 60 Gy) using conventional fractionation, with or without concurrent chemotherapy. Regarding re-irradiation technique, conventional radiotherapy was employed in 20 studies ($n = 1024$), SRS in 23 studies ($n = 1080$), and FSRT in 27 studies ($n = 1198$). Overall baseline characteristics for outcome and explanatory variables are presented in Table 2. Across all studies, the median OS from recurrence was 10.8 months (range, 5.3–30) and the mean radionecrosis rate was 4.6% (range, 0–31.3%) (Table 2). For the individual groups, unadjusted mean OS was 10 months, 12.1 months, and 10.6 months and unadjusted mean radionecrosis rate was 0.9%, 10.6%, and 3.3% for the conventional, SRS, and FSRT groups, respectively (Table 3). OS, radionecrosis, and PTV were not reported in 2 (3%), 11 (15%), and 25 (35%) studies, respectively.

Median re-irradiation EQD2 was 48.1 Gy (range, 20–110 Gy) and median total EQD2 was 108.1 Gy (range, 80–167 Gy). The median of the median PTV volume was 21.6 ml (range, 1.22–424 ml). Associations between the explanatory variables according to re-irradiation technique are summarized in Table 4. There was a statistically significant difference in cumulative EQD2, re-irradiation EQD2, dose per fraction, and median PTV between treatment groups ($P < .0001$).

The results of the multivariate analysis are summarized in Table 5. Re-irradiation EQD2 and re-irradiation dose per fraction were independently substituted for total cumulative EQD2 in the multivariate models for OS and radionecrosis because these distinctions are clinically

relevant. There were no concerns for collinearity between explanatory variables. There was a statistically significant difference in OS after re-irradiation according to treatment technique after adjusting for median age, total EQD2, median interval, and median PTV. This relationship remained when assessing re-irradiation EQD2 alone ($P < .0001$). The adjusted mean OS was 12.2 months (95% CI, 11.8–12.5) after SRS, 10.1 months (95% CI, 9.7–10.5) after FSRT, and 8.9 months (95% CI, 8.4–9.4) after conventional radiotherapy ($P < .0001$). Improved OS after re-irradiation was also associated with a greater interval between initial and repeat radiotherapy (OS gain of 0.25 months [~8 days] per month interval) ($P < .0001$).

There was a statistically significant association between radionecrosis rate and radiotherapy technique when adjusted for median age, total cumulative EQD2, median interval, and median PTV. The adjusted mean radionecrosis rate was 7.1% (95% CI, 6.6–7.7) for FSRT, 6.1% (95% CI, 5.6–6.6) for SRS, and 1.1% (95% CI, 0.5–1.7) for conventional radiotherapy. Radionecrosis rate after re-irradiation increased by 0.1% per Gy increase in total EQD2. Radionecrosis rate decreased with increasing interval between initial and repeat radiotherapy (reduction of 0.23% to 0.48% per month interval) ($P < .0001$).

There was no significant association between re-irradiation dose per fraction and OS ($P = .34$) or between re-irradiation dose per fraction and radionecrosis ($P = .43$); however, it was a valid confounder of the relationship between radiotherapy technique and the 2 outcome variables in their respective multivariate analyses. Increasing PTV volume at re-irradiation was associated with shorter

Table 1 Studies Included for Analysis. * = Prospective Studies ** = Randomized Trial

Author	Year	Type	Sample size (n) Total/ Grade IV	Age (years)	Initial XRT (Gy)		Re-irradiation (Gy)		Cumulative (Total) EQD2 (Gy)	Median interval (months)	Median PTV (ml)	Median Overall Survival (months)	Radionecrosis (%)		
					Total dose	Dose per fraction	Total dose	Dose per fraction							
Arcicasa ^{1*}	1999	Conventional	24	NR	44	60	2	34.5	1.5	30.2	90.2	14	NR	8.5	0
Neider ^{1*}	1999	Conventional	32	21	44	58.5	1.3	45.5	1.3	37.5	85.8	20	NR	6.6	6.25
Verninga ¹	2001	Conventional	22	17	34	60	2	46	2	46	106	32.8	NR	11.3	4.54
Combs ⁷	2005	Conventional	40	0	42	59.4	2	36	2	36	95.4	34.5	56.2	16	0
Combs ¹	2005	Conventional	101	59	50	60	2	36	2	36	96	19.14	49.3	11.32	1
Combs ¹	2005	Conventional	53	51	55	57	2	36	2	36	93	10	49	8	0
Adkison ^{19*}	2011	Conventional	76	0	45.5	59.4	2	50	2	50	109.4	18.2	369.2	10.4	0
Maier-Hauff ^{1*}	2011	Conventional	59	59	55.7	NR	NR	30	2	30	-	NR	46.5	13.4	0
Niyazi ¹⁷	2012	Conventional	30	22	51.5	60	2	36	2	36	96	NR	NR	NR	0
Niyazi ²⁰	2012	Conventional	39	30	51	60	2	36	2	36	96	21.4	NR	7.7	NR
Sholtyssek ²¹	2013	Conventional	64	11	53.4	60	2	36	2	36	96	13.4	110.4	NR	0
Niyazi ²²	2013	Conventional	58	46	52	60	2	36	2	36	96	21.4	NR	11.4	0
Osman ²³	2014	Conventional	29	20	42.1	60	2	36	2	36	96	13	NR	7.8	0
Fleiger ^{24*}	2014	Conventional	71	52	53	60	2	36	2	36	96	NR	NR	10.8	0
Niyazi ²⁵	2014	Conventional	31	25	51	60	2	36	2	36	96	34	118.1	11.5	NR
Wick ^{26***}	2014	Conventional	91	91	57.6	NR	NR	36	2	36	-	NR	NR	6.9	NR
Magnussen ²⁷	2014	Conventional	23	23	53	60	2	54	2	54	114	11.8	424	14.7	0
Aktan ²⁸	2015	Conventional	21	18	48	60	2	54	2	54	114	39.4	NR	9	0
Schnell ²⁹	2016	Conventional	105	85	48.5	60	2	36	2	36	96	17.7	105.8	10.3	0
Jeongshim ³⁰	2016	Conventional	29	21	42.5	59.4	2	45	1.8	42.8	102.2	30.5	NR	13.7	10.34
Alexander ¹	1992	SRS	25	16	45	59.4	2	13	13	48.8	108.2	14	10	9	12
Hall ¹⁷	1995	SRS	35	26	47	60	1.8	20	20	110	167	8	28	6.5	14
Shreive ¹	1995	SRS	86	86	46	NR	NR	13	13	48.8	-	10.3	10.1	10.2	22
Larson ¹	1996	SRS	93	66	49.9	NR	NR	16	16	72	-	NR	6.7	13	NR
Kondziolka ¹	1997	SRS	42	19	47.8	60	2	15.2	15.2	65.4	125.4	14.3	6	30	7.1
Van Kampen ^{17*}	1998	SRS	27	27	NR	60	2	16	16	72	132	9.6	21	9	0
Cho ¹	1999	SRS	46	27	48	60	1.8	17	17	80.8	137.8	10	30	11	4.3
Park ¹	2000	SRS	23	23	53	NR	NR	15	15	63.8	-	NR	9.9	10.3	NR
Larson ^{1*}	2002	SRS	26	14	48.8	NR	NR	15	15	63.8	-	NR	12.3	12.95	NR
Combs ¹	2005	SRS	32	32	56	54	2	15	15	63.8	117.8	10	10	10	0

Table 1 Continued

Author	Year	Type	Sample size (n) Total / Grade IV	Age (years)	Initial XRT (Gy)		Re-irradiation (Gy)		Cumulative (Total) EQD2 (Gy)	Median interval (months)	Median PTV (ml)	Median Overall Survival (months)	Radionecrosis (%)			
					Total dose	Dose per fraction	Total dose	Dose per fraction								
Hsieh ¹	2005	SRS	26	26	58	60	2	60	12	12	42	102	NR	21.6	10	31.3
Mahajan ^{1*}	2005	SRS	41	41	54	60	2	60	NR	NR	-	-	10	4.7	11	NR
Kong ^{2*}	2008	SRS	114	65	49	60	2	60	16	16	72	132	NR	10.6	16.25	24.4
Patel ¹	2009	SRS	26	26	53	60	2	60	18	18	90	150	12.5	10.4	8.4	NR
Villavicencio ¹⁷	2009	SRS	26	26	56.4	60	2	60	20	10	60	120	10	7	7	NR
Pouratian ¹⁷	2009	SRS	26	26	60.1	60	2	60	17	17	80.8	140.8	NR	21.3	9.4	0
Cuneo ³¹	2012	SRS	63	49	47	60	2	60	15	15	63.8	123.8	NR	4.8	10	10
Skeie ³²	2012	SRS	51	51	51	60	2	60	12.2	12.2	43.3	103.3	11	12.4	12	0
Park ³³	2012	SRS	44	44	64	60	2	60	15	15	63.8	123.8	16.8	9.5	12.2	0
Elliott ³⁴	2012	SRS	26	16	60.4	60	2	60	15	15	63.8	123.8	5.8	1.2	13.5	8
Conti ^{35*}	2012	SRS	23	23	58	60	2	60	20	10	60	120	7	13.8	12	4.3
Martinez Carillo ³⁶	2014	SRS	51	26	48	60	2	60	18	18	90	150	13.8	6	10	10
Pinzi (sSRS) ³⁷	2015	SRS	42	NR	51	58	2	58	15	15	63.8	121.8	11	2	11.5	6
Pinzi (mSRS) ³⁷	2015	FSRT	86	NR	51	58	2	58	23	7.66	55.5	113.5	11	11	11.5	6
Glass ^{1*}	1997	FSRT	20	13	44	NR	NR	-	42	NR	-	-	8	NR	13.7	15
Shepherd ¹	1997	FSRT	33	0	37	55	1.8	52.25	35	5	61.25	113.5	29	NR	10.7	12
Cho ¹⁷	1999	FSRT	25	15	53	60	1.8	57	37.5	2.5	42.1875	99.1875	19	NR	12	5
Hudes ^{1*}	1999	FSRT	20	19	52	60	1.8	57	24-35	3-3.5	48.2 max	105.2 max	3.1	NR	10.5	0
Seich ¹	2000	FSRT	21	14	54	60	2	60	25	5.00	43.75	103.75	11	NR	6.7	0
Lederman ^{1*}	2000	FSRT	88	88	56	60	1.8	57	24	6	48	105	7.8	NR	7	8
Grosu ^{1*}	2005	FSRT	44	35	50	60	1.8-3	57-75	30	5	52.5	109.5-127.5	16	NR	8	0
Wurm ^{1*}	2006	FSRT	25	20	45	60	1.8	57	25-30	5	43.75-52.5	100.75-109.5	12.8	NR	14.5	0
Kohshi ^{1*}	2007	FSRT	25	11	46	60	2	60	22	2.8	26.1	86.1	11	NR	15.5	28
Fokas ^{1*}	2009	FSRT	53	53	53	54	2	54	30	3	37.5	91.5	NR	35.01	9	0
Gutin ^{1*}	2009	FSRT	25	20	56	59.4	1.8	56.4	30	6	60	116.4	14.5	34	12.5	0
Henke ³⁸	2009	FSRT	31	29	50	59	2	59	20	5	35	94	18	NR	5.3	0
Fogh ¹	2010	FSRT	147	105	53	60	2	60	35	3.5	48.1	108.1	8	NR	11	0
Minnit ^{39*}	2011	FSRT	36	36	56	60	2	60	37.5	2.5	42.2	102.2	14	32.1	9.7	8
Mckenzie ^{39*}	2013	FSRT	35	29	62	59.4	1.8	56.4	30	6	60	116.4	NR	8.54	8.6	9
Shapiro ⁴⁰	2013	FSRT	24	20	56	59.4	1.8	56.4	30	6	60	116.4	12.6	35	12.2	0

Table 1 Continued

Author	Year	Type	Sample size (n) Total/ Grade IV	Age (years)	Initial XRT (Gy)		Re-irradiation (Gy)		Cumulative (Total) EOD2 (Gy)	Median interval (months)	Median PTV (ml)	Median Overall Survival (months)	Radionecrosis (%)			
					Total dose	Dose per fraction	Total dose	Dose per fraction								
Minniti ⁴⁷	2015	FSRT	54	42	54	60	2	60	25	5	43.8	103.8	14	33.1	9.6	5
Ertas ⁴¹	2014	FSRT	42	30	52	60	2	60	18	6	36	96	19	42	8.85	4.7
Miwa ^{42*}	2014	FSRT	21	21	53.9	60	2	60	30	6	60	120	12	27.4	11	9.5
Yacizi ^{43*}	2014	FSRT	37	37	NR	60	2	60	30	6	60	120	NR	NR	10.6	2.7
Palmer ⁴⁴	2015	FSRT	231	208	54.125	60	2	60	35	3.5	48.1	108.1	10.2	NR	10.77	0
Antonj ⁴⁵	2015	FSRT	20	12	55.7	60	2	60	31.2	6.25	64.4	124.4	18.3	2.71	15.6	NR
Scorsetti ⁴⁶	2015	FSRT	21	21	50	60	2	60	25	5	43.8	103.8	13	NR	11	0
Dincoglan ⁴⁸	2015	FSRT	28	28	55.6	60	2	60	25	5	43.8	103.8	11.2	36.5	10.3	11
Zwirner ⁴⁹	2016	FSRT	36	NR	55.9	60	2	60	NR	NR	-	-	NR	55.1	10.7	0
Navaria ⁵⁰	2016	FSRT	25	13	50	60	2	60	25	5	43.8	103.8	NR	35	18	0
Pinzi (mSRS) ³⁷	2015	FSRT	86	NR	51	58	2	58	23	7.66	55.5	113.5	11	11	11.5	6
Glass ^{1*}	1997	FSRT	20	13	44	NR	NR	-	42	NR	-	-	8	NR	13.7	15
Shepherd ¹	1997	FSRT	33	0	37	55	1.8	52.25	35	5	61.25	113.5	29	NR	10.7	12
Cho ¹⁷	1999	FSRT	25	15	53	60	1.8	57	37.5	2.5	42.1875	99.1875	19	NR	12	5
Hudes ^{1*}	1999	FSRT	20	19	52	60	1.8	57	24-35	3-3.5	48.2 max	105.2 max	3.1	NR	10.5	0
Selch ¹	2000	FSRT	21	14	54	60	2	60	25	5.00	43.75	103.75	11	NR	6.7	0
Lederman ^{1*}	2000	FSRT	88	88	56	60	1.8	57	24	6	48	105	7.8	NR	7	8
Grosu ^{1*}	2005	FSRT	44	35	50	60	1.8-3	57-75	30	5	52.5	109.5-127.5	16	NR	8	0
Wurm ^{1*}	2006	FSRT	25	20	45	60	1.8	57	25-30	5	43.75-52.5	100.75-109.5	12.8	NR	14.5	0
Kohshi ^{1*}	2007	FSRT	25	11	46	60	2	60	22	2.8	26.1	86.1	11	NR	15.5	28
Folkas ^{1*}	2009	FSRT	53	53	53	54	2	54	30	3	37.5	91.5	NR	35.01	9	0
Gutin ^{1*}	2009	FSRT	25	20	56	59.4	1.8	56.4	30	6	60	116.4	14.5	34	12.5	0
Henke ³⁸	2009	FSRT	31	29	50	59	2	59	20	5	35	94	18	NR	5.3	0
Fogh ¹	2010	FSRT	147	105	53	60	2	60	35	3.5	48.1	108.1	8	NR	11	0
Minniti ^{39*}	2011	FSRT	36	36	56	60	2	60	37.5	2.5	42.2	102.2	14	32.1	9.7	8
Mckenzie ^{39*}	2013	FSRT	35	29	62	59.4	1.8	56.4	30	6	60	116.4	NR	8.54	8.6	9
Shapiro ⁴⁰	2013	FSRT	24	20	56	59.4	1.8	56.4	30	6	60	116.4	12.6	35	12.2	0
Minniti ⁴⁷	2015	FSRT	54	42	54	60	2	60	25	5	43.8	103.8	14	33.1	9.6	5

Table 1 Continued

Author	Year	Type	Sample size (n) Total / Grade IV	Age (years)	Initial XRT (Gy)		Re-irradiation (Gy)		Cumulative (Total) EOD2 (Gy)	Median interval (months)	Median PTV (ml)	Median Overall Survival (months)	Radionecrosis (%)	
					Total dose	Dose per fraction	Total dose	Dose per fraction						
					EOD2	EOD2	Total dose	EOD2						
Ertas ⁴¹	2014	FSRT	42 / 30	52	60	2	60	18	6	36	19	42	8.85	4.7
Miwa ^{42*}	2014	FSRT	21 / 21	53.9	60	2	60	30	6	60	12	27.4	11	9.5
Yaciz ^{43*}	2014	FSRT	37 / 37	NR	60	2	60	30	6	60	NR	NR	10.6	2.7
Palmer ⁴⁴	2015	FSRT	231 / 208	54.125	60	2	60	35	3.5	48.1	10.2	NR	10.77	0
Antoni ⁴⁵	2015	FSRT	20 / 12	55.7	60	2	60	31.2	6.25	64.4	18.3	2.71	15.6	NR
Scorsetti ⁴⁶	2015	FSRT	21 / 21	50	60	2	60	25	5	43.8	13	NR	11	0
Dincoglan ⁴⁸	2015	FSRT	28 / 28	55.6	60	2	60	25	5	43.8	11.2	36.5	10.3	11
Zwirner ⁴⁹	2016	FSRT	36 / NR	55.9	60	2	60	NR	NR	-	NR	55.1	10.7	0
Navaria ⁵⁰	2016	FSRT	25 / 13	50	60	2	60	25	5	43.8	NR	35	18	0
Miwa ^{42*}	2014	FSRT	21 / 21	53.9	60	2	60	30	6	60	12	27.4	11	9.5
Yaciz ^{43*}	2014	FSRT	37 / 37	NR	60	2	60	30	6	60	NR	NR	10.6	2.7
Palmer ⁴⁴	2015	FSRT	231 / 208	54.125	60	2	60	35	3.5	48.1	10.2	NR	10.77	0
Antoni ⁴⁵	2015	FSRT	20 / 12	55.7	60	2	60	31.2	6.25	64.4	18.3	2.71	15.6	NR
Scorsetti ⁴⁶	2015	FSRT	21 / 21	50	60	2	60	25	5	43.8	13	NR	11	0
Dincoglan ⁴⁸	2015	FSRT	28 / 28	55.6	60	2	60	25	5	43.8	11.2	36.5	10.3	11
Zwirner ⁴⁹	2016	FSRT	36 / NR	55.9	60	2	60	NR	NR	-	NR	55.1	10.7	0
Navaria ⁵⁰	2016	FSRT	25 / 13	50	60	2	60	25	5	43.8	NR	35	18	0

Abbreviations: XRT, radiotherapy; EOD2, equivalent dose in 2Gy per fraction; PTV, planning target volume; SRS, stereotactic radiosurgery; FSRT, fractionated stereotactic radiotherapy.

Table 2 Overall Outcome and Explanatory Variable Characteristics

Variable (n = number of patients)	Median	Min	Max	Standard Deviation	IQR
Median overall survival (months) (n = 3190)	10.8	5.3	30	3.2	2.5
Radionecrosis (%) (n = 2860)	0 (Mean = 4.6%)	0	31.3	7.26	8
Median age (years) (n = 3302)	52	34	64	4.7	5.6
Median interval (months) (n = 2494)	13	3.1	39.4	6.5	8
Total EQD2 (Gy) (n = 2827)	108.1	80	167	15.5	20.4
Re-irradiation EQD2 (Gy) (n = 3205)	48.1	20	110	15.6	24
Dose per fraction (Gy) (n = 3205)	3.5	1.3	20	5.6	11
Median PTV (ml) (n = 1961)	21.6	1.22	424	81.0	39

Abbreviations: XRT, radiotherapy; EQD2, equivalent dose in 2Gy per fraction; PTV, planning target volume; SRS, stereotactic radiosurgery; FSRT, fractionated stereotactic radiotherapy.

Table 3 Unadjusted Outcome Variable Characteristics by Treatment Technique

Variable (n = number of patients)	Type	Median (Mean)	Min	Max	Standard Deviation	IQR	Overall P value	Pairwise P value
Median Overall Survival (months) (n = 3190)	Conventional	10.4 (10)	5.3	16	2.6	3.6	<.0001	<.01 vs SRS <.01 vs FSRT
	SRS	11.5 (12.1)	6.5	30	4.3	3.0		<.01 vs FSRT
	FSRT	10.8 (10.6)	6.7	18	2.14	1.4		-
Radionecrosis (%) (n = 2860)	Conventional	0 (0.9)	0	10.3	2.1	1.0	<.0001	<.01 vs SRS <.01 vs FSRT
	SRS	8.0 (10.6)	0	31.3	9.1	17.7		<.01 vs FSRT
	FSRT	0 (3.3)	0	28.0	5.5	5.0		-

Abbreviations: IQR, interquartile range; SRS, stereotactic radiosurgery; FSRT, Fractionated stereotactic radiotherapy.

OS (reduction of 0.014 months per ml PTV) ($P < .0001$) and a lower radionecrosis rate (reduction of 0.01% per ml PTV) ($P < .0001$). Age was not associated with OS but was associated with radionecrosis rate (rate decreased by 0.37% to 0.78% for each year older in age) ($P < .0001$). Explanatory variables accounted for 27% to 30% of the variability in OS and 55% to 59% in radionecrosis rate.

Discussion

This study demonstrates that survival after re-irradiation for recurrent high-grade glioma is similar to that observed following other treatments and that the risk of radionecrosis is low overall. There was a significant association between re-irradiation radiotherapy technique and both OS and radionecrosis. OS was longest in the SRS group, followed by the FSRT and conventional radiotherapy groups. FSRT and SRS were associated with higher rates of radionecrosis whether assessing total EQD2, median re-irradiation EQD2, or median re-irradiation dose per fraction and after adjustment for median age, median interval between initial and repeat radiotherapy, and median

PTV. In the multivariate analysis, increasing total EQD2 and decreasing PTV were associated with improved OS. Although these reached statistical significance, the clinical relevance is uncertain because the magnitude of potential benefit is limited within the range of explanatory data analyzed. Assessment for effects in the PTV range 10 to 106 ml (median SRS and conventional values) is likely to be most reliable and is a clinically common range. The impact of re-irradiation EQD2 and re-irradiation dose per fraction were not significantly associated with improved OS after adjusting for radiotherapy technique and median PTV. This suggests further dose escalation is unlikely to be of clinical benefit, which is consistent with data in the front-line setting.¹⁶

Prolonged interval between initial and repeat radiotherapy was associated with improved OS, which may indicate a more favorable disease biology. Larger PTV was associated with inferior OS and may reflect a more advanced stage of recurrence. The superior survival of patients in studies pertaining to SRS were likely reflective of healthier patients with smaller lesions who may have received additional chemotherapy and surgical options. Our inclusion criteria permitted studies in which patients received other treatment modalities and the heterogeneity in cases

Table 4 Unadjusted Explanatory Variable Characteristics by Treatment Technique

Variable (n = patients)	Type	Median	Min	Max	IQR	Overall P value	Pairwise P value
Median age (years) (n = 3302)	Conventional	50.0	34	57.6	6.9	.06	.18 vs SRS <.01 vs FSRT
	SRS	49.9	45	64.0	5.0		<.01 vs FSRT
	FSRT	53.9	37	62.0	2.1		-
Median interval (months) (n = 2494)	Conventional	19.1	10	39.4	7.4	<.0001	<.01 vs SRS <.01 vs FSRT
	SRS	11	5.8	16.8	2.5		<.01 vs FSRT
	FSRT	10.6	3.1	29.0	6.0		-
Cumulative EQD2 (Gy) (n = 2827)	Conventional	96	80	114	0	<.0001	<.01 vs SRS <.01 vs FSRT
	SRS	123.8	102	167	14.3		<.01 vs FSRT
	FSRT	108.1	86.1	103.8	4.4		-
Re-irradiation EQD2 (Gy) (n = 3205)	Conventional	36	20	54	0	<.0001	<.01 vs SRS <.01 vs FSRT
	SRS	63.8	42	110	16.5		<.01 vs FSRT
	FSRT	48.1	26.1	64.4	4.4		-
Dose per fraction (Gy) (n = 3205)	Conventional	2.0	1.3	2	0	<.0001	<.01 vs SRS <.01 vs FSRT
	SRS	15.0	7.7	20	3		<.01 vs FSRT
	FSRT	5	2.5	6.3	2.5		-
Median PTV (ml) (n = 1961)	Conventional	105.8	46.5	424	61.1	<.0001	<.01 vs SRS <.01 vs FSRT
	SRS	10.1	1.22	30	4.3		<.01 vs FSRT
	FSRT	35	2.7	55.1	9.9		-

Abbreviations: IQR, interquartile range; SRS, stereotactic radiosurgery; FSRT, fractionated stereotactic radiotherapy; EQD2, equivalent dose in 2Gy per fraction; PTV, planning target volume.

of systemic treatment, interval surgery, and other comorbidities are likely to have a significant but unquantifiable contribution to OS.

SRS and FSRT were associated with a higher risk of radionecrosis than conventional radiotherapy. The magnitude of the range in total EQD2 observed in the data (80–167 Gy) could equate to a clinically meaningful difference in radionecrosis between the re-irradiation techniques of approximately 8.7%. Associations between radionecrosis and PTV and age were clinically small and potentially confounded by expected inferior OS because individual patient data is lacking. Accounting for the expected increased conformality of SRS and FSRT compared to conventional radiotherapy, their greater re-irradiation, and total EQD2 values, we speculate that total dose carries greater weight in the risk for radionecrosis than PTV or fraction size. This has been asserted in previous studies where cumulative doses of 100 Gy were associated with a greater rate of radionecrosis.^{14,17} In this analysis, 11 studies did not report radionecrosis data and only 5 of 28 (18%) studies observing radionecrosis included patients treated to a median total EQD2 dose below 100 Gy.

There are certain limitations to this analysis, which lacks individual patient data¹⁵ and is based on predominantly retrospective and small prospective studies. Explanatory variables account for approximately 27% and 55% of the

observed variability in OS and radionecrosis data, respectively, suggesting that additional uncontrolled factors may confound these associations such as performance status, comorbidities, and additional treatments including interval surgery and/or systemic therapy. Combining WHO grade III and IV recurrent gliomas in this analysis is justifiable because initial radiotherapy dose and treatment options at recurrence are similar, but OS at recurrence may differ according to histological and molecular information including *IDH* mutation and *MGMT* promoter methylation status.⁷ The validity of the linear quadratic model when applied to high doses per fraction is uncertain,¹⁸ but was a practical requirement for data aggregation and analysis. While survival outcomes are important, data relating to effects on functional independence, quality of life, and steroid dependence is lacking. Whether the differences in survival identified in this analysis represent true differences between treatment techniques or underlying selection biases is unclear. The diagnostic accuracy of differentiating between radiation necrosis and tumor recurrence is challenging.⁵¹ Conventional MRI is unable to differentiate between recurrence, early progression, or treatment effect; however, it is often the most common diagnostic modality used in practice in combination with clinical assessment. Readers are directed to Parvez et al (2014), which comprehensively discusses various diagnostic parameters and modalities that can be utilized to more

Table 5 Multivariate Analysis

	Median age	Median interval (months)	Total EQD2 (Gy)	Re-irradiation EQD2 (Gy)	Dose per fraction (Gy)	PTV (ml)	Type
Model 1 (MOS)	0.08-month decreased survival [95% CI, 0.03–0.13 months less] $P = .0019$	0.25-month increased survival [95% CI, 0.01–0.04 months greater] $P < .0001$	0.03-month increased survival [95% CI, 0.01–0.04 months greater] $P = .0004$	-	-	0.014-month decreased survival [95% CI, 0.01–0.02 months less] $P < .0001$	*Conventional as reference SRS 3.8 month increased survival [95%CI, 3.0–4.6 months greater] FSRT 1.5 month increased survival [95%CI, 0.9–2.2 months greater] $P < .0001$
Model 2 (MOS)	0.02-month decreased survival [95% CI, 0.02–0.07 months less] $P = .30$ [Non-confounder]	0.28-month increased survival [95% CI, 0.24–0.32 months greater] $P < .0001$	-	0.014-month decreased survival [95% CI, 0.0003 months greater–0.03 less] $P = .055$ [Confounder]	-	0.014-month decreased survival [95% CI, 0.01–0.02 months less] $P < .0001$	*Conventional as reference SRS 3.2 months increased survival [95%CI, 2.5–4.0 months greater] FSRT 1.2 months increased survival [95%CI 0.5–1.8 months greater] $P < .0001$
Model 3 (MOS)	0.02-month decreased survival [95% CI, 0.07 months less–0.02 greater] $P = .28$ [Non-confounder]	0.28-month increased survival [95% CI, 0.24–0.32 months greater] $P < .0001$	-	-	0.04-month decreased survival [95% CI, 0.1 months less–0.03 greater] $P = .34$ [Confounder]	0.014-month decreased survival [95% CI, 0.01–0.02 months less] $P < .0001$	*Conventional as reference SRS 3.2 months increased survival [95%CI, 2.1–4.3 months greater] FSRT 1.1 months increased survival [95%CI, 0.5–1.8 months greater] $P < .0001$
Model 4 (RN)	0.37% decreased rate [95% CI, 0.3–0.41 less] $P < .0001$	0.23% decreased rate [95% CI, 0.19–0.27 less] $P < .0001$	0.10% increased rate [95% CI, 0.09–0.11 greater] $P < .0001$	-	-	0.01% decreased rate [95%CI 0.009–0.013 less] $P < .0001$	*Conventional as reference SRS 0.4% increased rate [95%CI, 0.2–1.0% greater] FSRT 4% increased rate [95%CI, 3.4 to 4.4 greater] $P < .0001$
Model 5 (RN)	0.78% decreased rate [95% CI, 0.73–0.84 less] $P < .0001$	0.48% decreased rate [95% CI, 0.42–0.55 less] $P < .0001$	-	0.03% increased rate [0.01–0.05% greater] $P \leq .0005$	-	0.01% decreased rate [95%CI 0.007–0.014 less] $P < .0001$	*Conventional as reference SRS 5.0% increased rate [95%CI, 4.1–5.9 greater] FSRT 6.0% increased rate [95% CI, 5.3–6.8 greater] $P < .0001$
Model 6 (RN)	0.78% decreased rate [95% CI, 0.72–0.84 less] $P < .0001$	0.48% decreased rate [95% CI, 0.42–0.54 less] $P < .0001$	-	-	0.03% decreased rate [95% CI, 0.13% less–0.06% greater] $P = .43$ [Confounder]	0.01% decreased rate [95% CI, 0.009–0.015 less] $P < .0001$	*Conventional as reference SRS 4.5% increased rate [95%CI, 3.2–5.9% greater] FSRT 5.8% increased rate [95%CI, 5.0–6.6% greater] $P < .0001$

accurately discern between radiological radiation necrosis and recurrence. Variability in the definition of radionecrosis used among studies used in this analysis could impact on the interpretability of the data presented. Prospective studies did not perform survival analyses of time-dependent radionecrosis development following completion of re-irradiation and these would be useful for future studies.

Although a potential survival benefit was associated with SRS re-irradiation when adjusting for confounding factors, cautious clinical judgement is required to select suitable patients for treatment in the context of tumor volume. Despite adjustments for PTV in the multivariate analysis, this comparison is only valid within a limited range of volumes where significant overlap for the treatment modalities exists in this analysis (ie, SRS PTV range 1.2 to 30 ml, median 10.1 ml). Patients with large volumes would not be considered appropriate for SRS due to an expected increased risk of toxicity. The median PTV values for each re-irradiation technique given in Table 4 may be considered an approximate guide for suitability based on the published literature. While there was an association between increasing treatment volume and reduced OS in the multivariate analysis, this represents an overall small magnitude of change; 0.014-month decreased survival with each ml increase in PTV.

SRS re-irradiation dose and treatment volume must both be considered with respect to the risk of radionecrosis. The median unadjusted radionecrosis rate for SRS was 8% for a median treatment volume of 10.1 ml and median fractional dose of 15 Gy. These values are consistent with those observed in the initial re-irradiation dose-finding SRS study for patients receiving doses ranging between 15 Gy for tumor volumes up to 33 ml (~40 mm diameter) and 24 Gy for tumor volumes less than 4 ml (~20 mm maximal diameter).⁵²

Overall, all 3 re-irradiation techniques are reasonable options for appropriately selected patients, with an acceptable and low rate of radionecrosis. Re-irradiation technique selection may be influenced by fixed factors such as size of recurrence and PTV volume. However, in the absence of randomized data and where genuine clinical equipoise exists, hypofractionated or SRS approaches may be preferred for appropriate tumor volumes, particularly if the slightly higher risk of radionecrosis is deemed acceptable.

In conclusion, this population-weighted, pooled, multiple regression analysis demonstrates that re-irradiation is a feasible treatment option for select patients with recurrent high-grade glioma and the rate of radionecrosis is acceptable. Overall, all 3 re-irradiation techniques have clinical utility based on tumor size and PTV. Future studies should incorporate histological, molecular, and patient performance data and focus on comparison of re-irradiation to other treatments for recurrent high-grade glioma. Studies should also report data describing patient-reported outcomes and quality of life after treatment.

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