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Original article

Patterns of re-irradiation for recurrent gliomas and validation of a prognostic score

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ABSTRACT

Purpose or objective: Re-irradiation is a generally accepted method for salvage treatment in patients with recurrent glioma. However, no standard radiation regimen has been defined. This study aims to compare the efficacy and safety of different treatment regimens and to independently externally validate a recently published reirradiation risk score.

Material and methods: We retrospectively analyzed a cohort of patients with recurrent malignant glioma treated with salvage conventionally fractionated (CFRT), hypofractionated (HFRT) or stereotactic radiotherapy (SRT) between 2007 and 2017 at the University Medical Centers in Utrecht and Groningen.

Results: Of the 121 patients included, 60 patients (50%) underwent CFRT, 22 (18%) HFRT and 39 (32%) SRT. The primary tumor was grade II-III in 52 patients and grade IV in 69 patients with median Overall Survival (mOS) since first surgery of 113 [Interquartile range: 53.2–137] and 39.7 [24.6–64.9] months respectively ($p < 0.01$). Overall, mOS from the first day of re-irradiation was 9.7 months [6.5–14.6]. No significant difference in mOS was found between the treatment groups. In multivariate analysis, the Karnofsky performance scale $\geq$70% ($p < 0.01$), re-irradiation for first recurrence ($p = 0.02$), longer time interval between RT start dates ($p < 0.01$) and smaller planning target volume ($p < 0.05$) were significant favorable prognostic factors. The reirradiation risk score was validated.

Conclusion: In our series, mOS after reirradiation was sufficient to justify use of this modality. Until a reliable treatment decision tool is developed based on larger retrospective research, the decision for re-irradiation schedule should remain personalized and based on a multidisciplinary evaluation of each patient.

The diagnosis of high grade glioma is usually associated with an extremely poor prognosis, with a median overall survival time for glioblastoma patients of 14.6 months [1,2]. Despite multimodality treatments, the local recurrence rate persists to be high (nearly 90% within 2 years) and mostly occurs adjacent to the original tumor bed [1,3]. Additionally, for tumors presenting as low grade gliomas (WHO grade II), ultimately transformation to a more malignant phenotype will occur and eventually recur at a median of 61 months after primary treatment [4,5].

No standard salvage treatment for recurrence has been defined [4,6,7]. Next to re-resection and chemotherapy, re-irradiation (ReRT) can be considered as a safe and effective option, leading to median overall survival (mOS) ranging from 7.7 to 11.5 months [8–14]. Due to small cohorts, anecdotal experience and local differences, the fractionation schedule and prescribed total dose vary among medical centers and countries. ReRT treatment regimens include conventionally fractionated radiotherapy (CFRT), moderate hypofractionated radiotherapy (HFRT) and stereotactic radiotherapy (SRT). Due to a high local dose, SRT is mostly limited to small lesions, while CFRT and HFRT could also be used for the treatment of larger lesions [15]. Usage of higher doses per fraction, as occurring with SRT and HFRT, increases the risk of side effects, especially in larger volumes and tumors located close to eloquent structures

Abbreviations: CFRT, Conventionally fractionated radiotherapy; $EQD2_{\alpha/\beta=10}$, Equivalent dose at fractionation of 2 Gray, α/β ratio assumed 10 for tumor tissue; $EQD2_{\alpha/\beta=2}$, Equivalent dose at fractionation of 2 Gray, α/β ratio assumed 2 for brain tissue; HFRT, Moderate Hypofractionated radiotherapy; HR, Hazard ratio; IQR, Interquartile range; KPS, Karnofsky's performance scale; mOS, Median overall survival; OS, Overall survival from first day of salvage radiation; PFS, Progression free survival time from first day of salvage radiation; PH, Proportional hazards; ReRT, Re-irradiation; SIB, Simultaneous-integrated boost; SRT, Stereotactic radiotherapy.

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[15,16]. A major advantage of SRT and HFRT is the reduction in overall treatment time.

There is no global consensus on the most efficacious regimen, because optimal balance between OS and quality of life is difficult to achieve. Most of the reported data have been restricted to retrospective single center studies with only one ReRT schedule. Few studies compared different ReRT regimens [10,11,17–19] and only one of them performed multivariate analysis [10,17]. A prognostic score could help to predict the overall effect of ReRT and facilitate decision making. In addition to the already existing and optimized prognostic score of Combs et al., Niyazi et al. introduced a new prognostic ReRT risk score. The score was based on a linear combination of age, Karnofsky's performance scale (KPS) and initial histology. A strength of this ReRT score is that patients were initially classified into two large groups of a development cohort existing of 353 patients and a validation cohort of 212 patients. The data from the validation cohort were not made available before the score had been developed. Therefore, the score could be independently validated direct by themselves in contrast to the (optimized) prognostic score of Combs et al. [8,17,20].

The purpose of our multicenter retrospective study was to compare the efficacy and safety of CFRT, HFRT and SRT regimens for recurrent gliomas. Additionally, this cohort was used to independently externally validate Niyazi's ReRT risk score [20].

Patients and methods

Patient selection

All adult patients diagnosed with recurrent WHO grade II, III or IV malignant glioma that underwent ReRT at University Medical Center Utrecht and University Medical Center Groningen from 2007 to 2017 were identified ($n = 124$). Treatment decisions were always made by multidisciplinary tumor boards. Patients were generally considered eligible for ReRT if a minimum of 6 months had elapsed since initial radiotherapy and KPS was at least 70. Deviations from these requirements for individual patients by the tumor board were allowed. Most patients were pretreated with re-resection or multiple lines of chemotherapy.

Three patients were excluded from analysis because evaluation of radiotherapy plans was not feasible due to usage of virtual software (VSIM) without target volume definitions ($n = 2$) or because less than 50% of prescribed fractionations were administered ($n = 1$).

Patient, tumor and treatment characteristics were retrospectively extracted from the electronic medical records. When the KPS at salvage therapy was not mentioned, it was categorically recalculated from correspondences and medical records (feasible for 90.1%). O6-methylguanine-DNA-methyltransferase (MGMT)-methylation, 1p/19q-deletion and Isocitrate dehydrogenase (IDH) 1-mutation genetic tests, were only performed in respectively 9.9%, 34.7% and 35.5% of the cases (see Appendix Table A.2 for details). Therefore genetic variables were not included for multivariate analysis. Approval for this study was obtained from local Medical Research Ethics Committees (project number 17/803 UMCU and 201700624 UMCG).

Treatment

The cohort was subdivided into three treatment categories, according to daily fraction size. CFRT was defined as a fractional dose up to 3 Gy, HFRT including 3 to 5 Gy and SRT 5 Gy or more, in analogy to Dong et al. [21] and Koontz et al. [22].

GTV was defined as the contrast-enhancing volume on contrast enhanced T1 MRI or FLAIR abnormality for grade II lesions ($n = 2$). For CFRT and HFRT, CTV was defined as GTV plus a 5–10 mm margin. PTV margin was 2–5 mm depending on fixation and treatment techniques. 99% of the PTV received at least 95% of the prescription dose (V95% > 99%) with accepted dose heterogeneity of 95% to 107% according to ICRU report 50/62. For SRT, CTV margin was 0–2 mm and PTV margin was 1 mm with (V100% > 95%) or (V80% > 99%) and permitted dose heterogeneity up to 130% of the prescription dose, or without an upper dose limit. For the three treatment categories, a typical treatment plan is shown in Fig. 1.

For all ReRT treatments, three-dimensional conformal radiation therapy, intensity modulated radiation therapy or volumetric modulated arc therapy were applied by 6-MV linear accelerators (Elekta Instrument AB, Stockholm, Sweden; Novalis, BrainLAB, Feldkirchen, Germany). When a simultaneous integrated boost (SIB) concept was used, the largest PTV was used for further analysis.

The equivalent dose at fractionation of 2 Gy (EQD2), was calculated using the Linear Quadratic Model. The α/β ratio was assumed 10 Gy for tumor and 2 Gy for brain tissue [23–26].

Follow-up

During ReRT, all patients were evaluated weekly by a radiation oncologist. Post treatment imaging was performed 3 months after completion of treatment, and thereafter every 3 months or otherwise on indication. Post ReRT, all decisions on further therapies were made in multidisciplinary boards.

End points

The primary endpoint was OS, defined as the time from start of ReRT until death from any cause, or censoring at the date of last follow-up when death had not occurred yet. Progression free survival (PFS), as secondary endpoint, was defined as time from start of ReRT to any radiographic evidence of disease progression, death from any cause, or censoring at the last date of follow-up. The other secondary endpoint, toxicity, was defined as acute toxicity and radionecrosis. Acute toxicity was classified according to the Radiation Therapy Oncology Group acute radiation morbidity of the brain [27]. Acute toxicity grades 0 and 1 were combined as "not disabling" toxicity. Toxicity grade 2 required medication changes. Severe toxicity grade 3 leads to hospitalization during or within one month after ReRT. Radionecrosis was recorded when radiologically suspected, with or without confirmation by biopsy.

Statistical analysis

Median OS and PFS were estimated based on the Kaplan–Meier estimator and compared between treatment groups with the log-rank test. Besides, multivariate Cox regression was performed. Other potential prognostic variables for OS were retrieved using univariate and multivariate Cox regression. Details of variable selection method for multivariate regression are described in Appendix A.1. Fisher's exact test was used to compare toxicity grades in the different treatment groups.

The ReRT risk score was defined by Niyazi et al. [20] as "ReRT risk score = $0.013\ Age + 0.25\ \delta WHO_{grade\ =\ IV} - 0.90\ \delta KPS_{\geq 70}$. It was derived for our patients excluding 12 patients lacking KPS. The score was evaluated graphically by the Kaplan–Meier estimator. Hazard ratios (HR) were calculated by Cox regression using the score as single covariate. Uno's C-index [28] was computed to assess the discrimination performance of the score. Tau was set on 70 months.

A p-value of <0.05 was considered significant for outcome measurements. Data management and analysis were mainly performed using *IBM SPSS statistics (version 23)*. Schoenfeld's residuals and Uno's C-index were computed using *R (version 3.31.)*.

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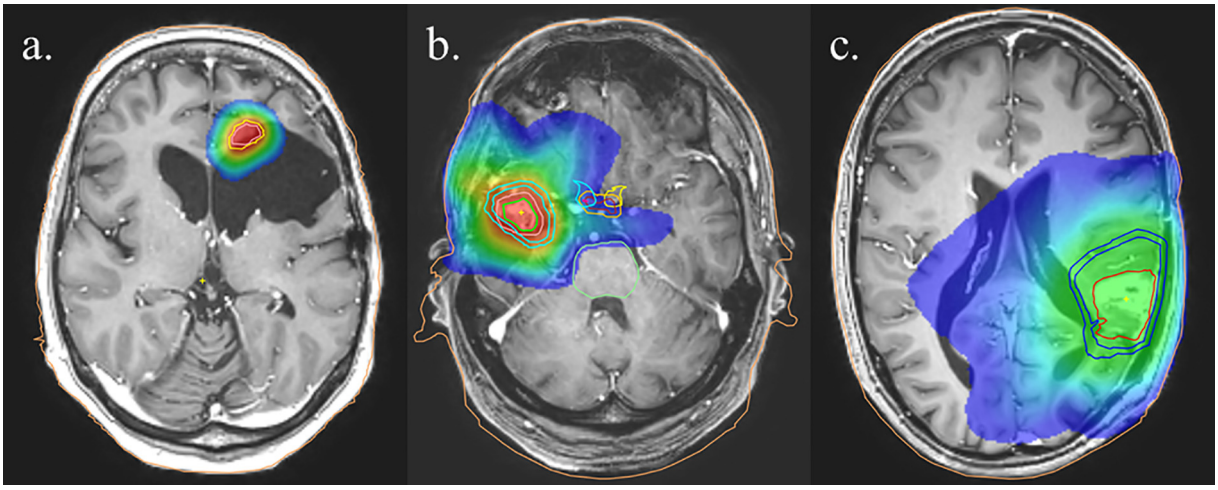

Fig. 1. Treatment plans for SRT (a), CFRT with a SIB (b) and HFRT (c). Showing a focal high dose due to stereotactic treatment and the SIB added to CFRT (a and b). Also a steeper dose fall-off outside the target for SRT is shown (a). The colors correspond to an $EQD2_{\alpha/\beta=2}$ of Blue >8 Gy; Green >30 Gy; Yellow >40 Gy; Red >50 Gy. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Results

Of 121 included patients with a glioma recurrence 60 patients (49.6%) received CFRT, 22 (18.2%) HFRT and 39 (32.2%) SRT. Thirty-two patients (26.4%) were originally grade II patients, 20 patients (16.5%) grade III and the remaining 69 (57.0%) were already grade IV glioma patients at first diagnosis. Most frequently used ReRT schedules for CFRT were 23 fractions of 2 Gy ($n = 21$) and 28 fractions of 1.8 (with or without SIB of 2.1 Gy, $n = 13$ and $n = 12$ respectively). For HFRT, 10 fractions of 3.5 Gy ($n = 17$). For SRT more various schemes were used, most often 6 fractions of 5 Gy ($n = 20$) and 3 fractions of 7 Gy ($n = 6$). An overview of used radiation schemes with corresponding EQD2 is shown in Appendix Table A.1.

Age ranged from 25 to 74 years. Patients treated with CFRT were younger ($p = 0.02$), had a slightly better KPS ($p = 0.06$), and their time interval from initial RT to ReRT was longer ($p < 0.01$). In the SRT group, PTV was considerably smaller ($p < 0.01$), WHO grade was more often IV at initial diagnose ($p < 0.01$) and recurrence ($p < 0.01$) and patients were more often treated with concomitant temozolomide at initial therapy ($p = 0.06$). Median cumulative $EQD2_{\alpha/\beta=10}$ was slightly higher for CFRT schedules ($p < 0.01$), while $EQD2_{\alpha/\beta=2}$ was higher for SRT regimens ($p < 0.01$). All other variables were similarly distributed over the treatment groups as shown in Table 1.

Median OS from the start of ReRT was 9.7 [IQR 6.5–14.6] months. For initial diagnosed glioblastoma mOS was 8.5 [6.5–11.6] and for lower graded tumors (WHO grade II-III) 11.3 [6.3–28.5] months. Median survival time from the date of primary diagnosis were respectively 39.7 [24.6–64.9] and 113 [53.2–137] months. In the CFRT, HFRT and SRT group mOS post re-RT was respectively 10.0 [6.9–17.6], 7.7 [5.7–10.3] and 9.7 [6.2–14.9] months. Overall, during follow-up 103 deaths (85.1%) were registered, see Fig. 2 for Kaplan–Meier's plots. No significant difference in OS between the ReRT regimens was found ($p = 0.17$). Pairwise comparison showed only a trend in favor of the CFRT group compared to the HFRT group ($p = 0.06$). Adjustment for KPS, time interval, PTV and initial WHO grade resulted in no significant difference between the treatment groups ($p = 0.79$).

Median PFS from the start of ReRT was 5.2 [IQR 3.5–9.4] months. For analysis of PFS, 10 cases were censored, 71 patients showed radiological progression and 40 patients deceased without progression registered on radiological imaging. Log-rank test showed a trend toward longer survival in the CFRT and SRT group ($p = 0.06$). After adjustment for time interval between RT start dates, a significant difference was only found in favor of the SRT group compared to the HFRT group (HR 1.93; 95% confidence interval (CI) 1.07–3.48; $p = 0.03$).

Toxicity as secondary endpoint could only be assessed for the UMC Utrecht dataset ($n = 65$). Eight patients (12.5%) developed severe acute toxicity (grade 3), scored as epileptic seizures (CFRT: $n = 6$ (19%), SRT: $n = 1$ (5%)) or increasing edema with unilateral paresis and urinary incontinence (HFRT: $n = 1$ (11%)). Only in 5 cases (7.7%) radionecrosis was reported after ReRT. All were based on MRI suspicion and including 2 cases confirmed by histology (both from the HFRT group). No significant difference was observed between the treatment groups (acute toxicity: $p = 0.45$; radionecrosis: $p = 0.30$).

The results of the univariate and multivariate analyses for prognostic factors for OS are shown in Table 2. In multivariate analysis, KPS $\geq$70% ($p < 0.01$), re-irradiation for the first recurrence ($p = 0.02$), longer time interval ($p < 0.01$) and smaller PTV ($p = 0.05$) were significant favorable prognostic factors of OS.

From the factors included in the ReRT risk score we could confirm WHO grade IV and KPS $\geq$70 as prognostic variables, while the HR of age was not statistically significant (see Table 2). In our cohort mOS in the good prognostic group was 14.6 [IQR 8.8–28.5] months, in the intermediate prognostic group 9.76 [6.8–12.9] months and in the poor prognostic group 5.32 [2.5–8.0] months. Kaplan–Meier's plots are shown in Fig. 3. In the Cox regression model, the intermediate group was used as a reference category. The HRs of the risk groups with good and poor rating were HR 0.61 (95% CI 0.37–0.999) ($p < 0.05$) and HR 2.93 (95% CI 1.64–5.22) ($p < 0.01$) respectively. Uno's C-index was 0.65 (95% CI 0.59–0.70). Table 3 shows the results of the ReRT risk score according to the different treatment groups, favorable to CFRT.

Discussion

Glioma patients have a poor prognosis and a high recurrence rate. Currently, re-irradiation is an accepted salvage therapy in selected patients at the time of recurrence, although chemotherapy rechallenge is chosen more often. However, no standard radiation regimen has been defined and various fractionation schemes are used in daily practice. Determining difference in effectiveness

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Table 1
Tumor and patient characteristics of all 121 patients. Data are displayed for the three dose-fractionation groups. Median values and ranges, as well as number and row percentages are shown. *P*-values are given based on Kruskal–Wallis' test (continuous data) or Fisher's exact test (categorical data).

Characteristic	CFRT (n = 60) n (%) Median (range)	HFRT (n = 22) n (%) Median (range)	SRT (n = 39) n (%) Median (range)	p-value
Age at ReRT (y)	50 (25–71)	59 (25–74)	57 (37–73)	0.019*
Gender				0.537
Male	40 (66.7%)	15 (68.2%)	22 (56.4%)	
Female	20 (33.3%)	7 (31.8%)	17 (43.6%)	
KPS at start ReRT[a]				0.064*
<50%	0 (0.0%)	0 (0.0%)	3 (8.3%)	
50–70%	4 (7.8%)	5 (22.7%)	4 (11.1%)	
≥70%	47 (92.2%)	17 (77.3%)	29 (80.6%)	
WHO grade at initial diagnosis				0.001*
GBM WHO grade IV	25 (41.7%)	13 (59.1%)	31 (79.5%)	
WHO grade III	16 (26.7%)	1 (4.5%)	3 (7.7%)	
WHO grade II	19 (31.7%)	8 (36.4%)	5 (12.8%)	
Tumor side at initial diagnosis				0.568
Left	24 (40.0%)	10 (45.5%)	14 (35.9%)	
Right	32 (53.3%)	10 (45.5%)	24 (61.5%)	
Bilateral	1 (1.7%)	1 (4.5%)	1 (2.6%)	
Central	3 (5.0%)	1 (4.5%)	0 (0%)	
Initial surgical procedure				0.456
Gross total resection	24 (40.0%)	7 (31.8%)	14 (35.9%)	
Subtotal resection	23 (36.6%)	12 (54.5%)	21 (53.8%)	
Biopsy	13 (21.7)	3 (13.6%)	4 (10.3%)	
TMZ concurrent at initial RT				0.059*
Yes	32 (53.3%)	14 (63.6%)	30 (76.9%)	
WHO Grade at recurrence[b]				0.003*
GBM WHO grade IV	32 (53.3%)	18 (81.8%)	32 (82.1%)	
WHO grade III	27 (45.0%)	3 (13.6%)	7 (17.9%)	
WHO grade II	1 (1.7%)	1 (4.5%)	0 (0.0%)	
Number of retreatment[c]				0.504
1	25 (41.7%)	13 (59.1%)	22 (56.4%)	
2	27 (45.0%)	5 (22.7%)	13 (33.3%)	
3	5 (8.3%)	3 (13.6%)	3 (7.7%)	
4	3 (5.0%)	1 (4.5%)	1 (2.6%)	
Location of recurrence				0.329
Local	48 (80.0%)	16 (72.7%)	28 (71.8%)	
New-location	8 (13.3%)	6 (27.3%)	10 (25.6%)	
Local and New	4 (6.7%)	0 (0.0%)	1 (2.6%)	
Surgery <2 months prior to ReRT				0.738
Yes	10 (16.7%)	3 (13.6%)	4 (10.3%)	
Time interval[d] (mo)	38.9 (8.1–188)	18.5 (3.0–104)	20.6 (8.7–214)	<0.001*
PTV (cc)	165.4 (13.7–554)	107.1 (5.0–343)	11.4 (0.8–125)	<0.001*
$EQD2_{\alpha/\beta=10}$[e] cumulative (Gy)	108 (87.1–120)	99.4 (85.6–99.4)	97.5 (79.3–110)	<0.001*
$EQD2_{\alpha/\beta=10}$ Initial RT (Gy)	60.0 (44.3–60.0)	60.0 (49.6–60.0)	60.0 (49.6–60.0)	0.021
$EQD2_{\alpha/\beta=10}$ ReRT (Gy)	49.6(29.5–60.0)	39.4 (28.0–39.4)	37.5 (29.8–50.0)	<0.001
$EQD2_{\alpha/\beta=2}$[f] cumulative (Gy)	106 (85.3–120)	108 (88.8–108)	113 (95.1–170)	<0.001
$EQD2_{\alpha/\beta=2}$ Initial RT (Gy)	60.0 (42.8–60.0)	60.0 (47.9–60.0)	60.0 (47.9–60.0)	0.333
$EQD2_{\alpha/\beta=2}$ ReRT (Gy)	47.9 (28.5–60.3)	48.1 (36.0–48.1)	52.5 (43.8–110)	<0.001

Abbreviations: CFRT: conventional fractionated radiotherapy; EQD2: equivalent dose at fractionation of 2 Gy; HFRT: hypofractionated radiotherapy; KPS: Karnofsky's performance scale; NS: not specified; PTV: planning target volume; RT: radiotherapy; ReRT: re-irradiation; SRT: stereotactic radiotherapy.

* Used in backward selection for the Cox-Proportional Hazard Model for overall survival.

[a] KPS was missing in 12 cases (CFRT: 9 cases, SRT: 3 cases).

[b] In 19 cases pathohistologically confirmed.

[c] Number of recurrences occurred before re-irradiation.

[d] Time interval between start date of initial radiotherapy and start date of re-irradiation.

[e] Calculated with $\alpha/\beta = 10$ for tumor tissue.

[f] Calculated with $\alpha/\beta = 2$ for brain tissue.

and toxicity of the various re-irradiation regimens may facilitate clinical decision-making and produce benefits for individual patients.

In this study, the mOS of 9.7 months (8.5 for initial glioblastoma and 11.3 months for grade II-III patients) was comparable to other reports including mixture of different histologic subtypes. Reported OS range from 7.7 to 11.5 months [9,11–15,20,29]. This study did not show a significant difference in OS between the three dose-fractionation regimens. Kaplan–Meier's estimators showed a trend toward better OS for CFRT compared to HFRT. This can be explained by the relatively good pre-treatment prognosis in the CFRT group admitted by the ReRT risk score. CFRT was more often prescribed to younger patients with a good performance score, large tumors, and a long time interval between radiotherapy treatments. SRT was preferred in small tumors and in patients with glioblastoma at first diagnosis. HFRT was more often selected in

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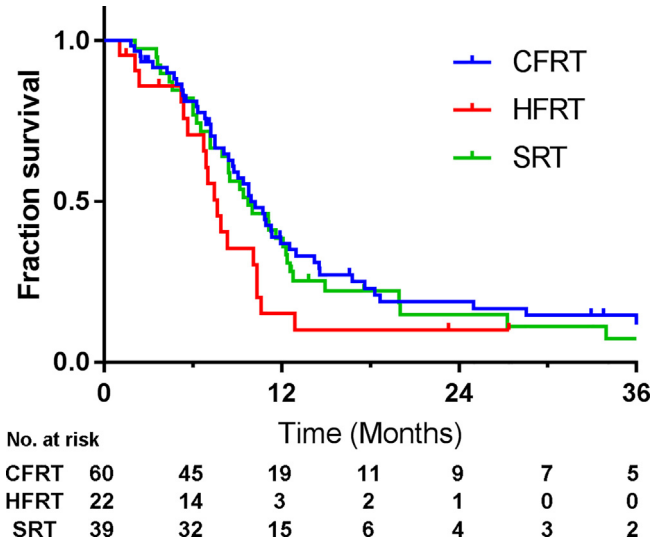

Fig. 2. Kaplan–Meier's curves showing overall survival from first day of re-irradiation (time in month) according to SRT (green line), HFRT (red line) and CFRT (blue line). Log-rank test was not significant ($p = 0.173$). Pairwise comparison was also not significant (CFRT vs HFRT $p = 0.060$; CFRT vs SRT $p = 0.735$; SRT vs HFRT $p = 0.162$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

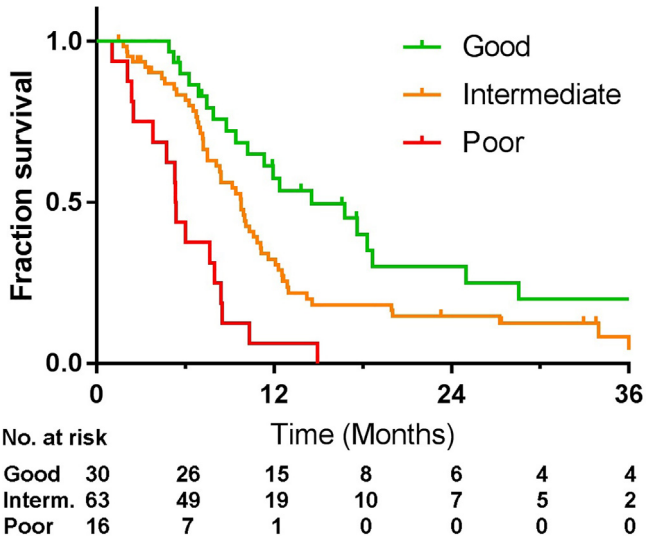

Fig. 3. Kaplan–Meier's curves showing overall survival from first day of re-irradiation (time in month) according to the good (blue line), intermediate (red line) and poor (green line) prognostic groups following Niyazi's reirradiation risk score. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

patients with larger tumors and a poor to intermediate prognosis. Few studies compared OS in various treatment regimens (see Table 4).

As suggested by the HRs, after correcting for time interval, PFS was significantly better for the SRT cohort compared to HFRT patients. Nevertheless, this finding should be interpreted with caution, since the date of progression is subject to measurement error and timing of measurement may result in an artifactual difference in progression dates. This is confirmed by the finding that radiological progression occurred mainly after 4 months corresponding to planned first MRI after ReRT. Currently, there is no reliable imaging method to distinguish between radionecrosis and progression, and biopsy is often not performed. Moreover, in practice generally no follow-up imaging is performed in case after clinical deterioration, therefore progression and radionecrosis are definitely underestimated. For 40 patients data on progression were missing and in those cases date of death was used as date of progression. However, normally, progression appears before death.

Overall, 8 patients (12.5%) developed severe acute toxicity. Only few other studies, including one phase-I prospective study, reported acute toxicity with need for hospitalization in comparable percentages [19,30]. Early reactions are usually reversible and therefore often assumed less relevant. However, higher toxicity-rates will potentially diminish quality of life. Five cases (7.8%) of radionecrosis were reported in our study. Mayer et al. [24]

Table 2
Univariate and multivariate Cox regression analysis of prognostic factors for overall survival in 121 patients receiving re-irradiation (16 censored, 20 cases with missing values). Data are expressed as hazard ratios and *p*-values.

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age at ReRT	1.015	0.997–1.033	0.112	1.012	0.990–1.031	0.280
Gender (♂ vs ♀)	0.964	0.643–1.444	0.857	–	–	–
KPS at ReRT (<70% vs ≥70%)	3.434	1.954–6.034	<0.001*	3.138	1.730–5.692	<0.001*
WHO Grade initial (<IV vs IV)	0.525	0.347–0.794	0.002*	0.807	0.403–1.613	0.543
Initial Surgery (Gross total†)				–	–	–
Subtotal	0.956	0.627–1.458	0.835	–	–	–
Biopsy	0.670	0.362–1.237	0.200	–	–	–
Tumor side (lateral vs central)	1.725	0.751–3.961	0.199	–	–	–
TMZ (no vs yes)	1.822	1.185–2.801	0.006*	–	–	–
Number of recurrence[a] (≥2 vs 1)	0.887	0.601–1.311	0.548	1.801	1.096–2.957	0.020*
WHO Grade recurrence (<IV vs IV)	0.487	0.309–0.768	0.002*	–	–	–
Surgery prior to ReRT[b] (no vs yes)	0.716	0.398–1.288	0.265	–	–	–
Time interval[c]	0.982	0.974–0.989	<0.001*	0.981	0.969–0.993	0.002*
PTV	1.002	1.000–1.004	0.027*	1.002	1.000–1.004	0.047*
$EQD2_{\alpha/\beta=10}$[d] cumulative	0.992	0.971–1.014	0.476	–	–	–

Abbreviations: CI: Confidence interval; EQD2: equivalent dose at fractionation of 2 Gy; HR: Hazard ratio; KPS: Karnofsky's performance scale; NS: not specified; PTV: planning target volume; RT: radiotherapy; ReRT: re-irradiation; TMZ: temozolomide concurrent at initial therapy.

* *p* value of <0.05 was considered significant.

† Reference group.

[a] Number of recurrences occurred before re-irradiation.

[b] Surgery within 2 months prior to re-irradiation.

[c] Time interval between start date of initial radiotherapy and start date of re-irradiation.

[d] Calculated with $\alpha/\beta = 10$ for tumor tissue.

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Table 3
Prognostic outcome of Niyazi's reirradiation risk score in 109 patients according to the three dose-fractionation groups. Count and column percentages are shown. The p-value is given based on Fisher's exact test.

ReRT risk score Prognostic group	CFRT (n = 51) n (%)	HFRT (n = 22) n (%)	SRT (n = 36) n (%)	Total n (%)	Deceased n	P-value
Good	22 (43.1%)	4 (18.2%)	4 (11.1%)	30 (27.5%)	23	0.008*
Intermediate	25 (49.0%)	13 (59.1%)	25 (69.4%)	63 (57.8%)	54	
Poor	4 (7.8%)	5 (22.7%)	7 (19.4%)	16 (14.7%)	16	

Abbreviations: CFRT: conventionally fractionated radiotherapy; HFRT: hypofractionated radiotherapy; ReRT: re-irradiation; SRT: stereotactic radiotherapy.
* p value of <0.05 was considered significant.

Table 4
Summary of re-irradiation studies for patients with recurrent gliomas comparing various treatment regimens.

	Schedules (no. of fractions × dose per fraction)	n	Treatment-group according to this study	OS (months)	Univariate analysis	Multivariate analysis
Kessel et al. (2017) [10,17]	18 × 2 Gy	23	CFRT	7.6	p = 0.018*	Ref.
	6 × 5 Gy	90	SRT	9.6		HR 1.91
	12 × 3 Gy	36	HFRT	6.7		HR 1.45
	23 × 2 Gy	29	CFRT	11.3		HR 2.35
						p = 0.038*[a]
Zwirner et al. (2017) [18]	15-25 × 2 Gy	11	CFRT	7.5	p = 0.06*	–
	1 × 12–20 Gy	4	SRT	10.0		
	5 × 4–5 Gy	36	HFRT	10.7		
Arvold et al. (2017) [11]	1 × 18–20 Gy	10	SRT	NR	NS	–
	6 × 5 Gy	24	SRT			
	10 × 3.5 Gy	14	HFRT			
	15 × 2.67 Gy	10	CFRT			
Cho et al. (1999) [15]	1 × 9–40 Gy	46	SRT	11	p = 0.32	–
	10–20 × 2–4.5 Gy	25	C/HFRT	12		
Vordermark et al. (2005)	5/4/2 × 4/5/10 Gy	8	HF/SRT	7.4	p = 0.051	
	5 × 6/6 × 5	11	SRT	11.1		

Abbreviations: CFRT: conventionally fractionated radiotherapy; HFRT: hypofractionated radiotherapy; HR: Hazard Ratio; NR: not reported; NS: not significant; OS: Overall survival; SRT: stereotactic radiotherapy.
* p value of <0.05 was considered significant.
[a] Covariates includes in multivariate model WHO grade; Age ≥<50 years; Time interval >≤12 months; KPS ≥<80%; neurological symptoms; Gender; PTV ≥<47 ml; Dose group.

reported that radionecrosis occurs at a cumulative $EQD2_{a/b = 2}$ >100 Gy and for stereotaxy after >135 Gy. In three of our cases $EQD2_{a/b = 2}$ was 108 Gy (CFRT: n = 1; HFRT: n = 2). In all cases time interval was more than 12 months. PTV ranged from 8.8 to 307 cc. Most larger retrospective studies do not report severe acute toxicity or radionecrosis at all [8,9,13,14]. However, some studies report high radionecrosis rates from 30–43% [15,31,32]. Reported differences in toxicity among studies could be assigned to differences in radiotherapy prescription and patient characteristics. However, the variation among studies is probably partly caused by insufficient detection in retrospective studies as well as different interpretations of follow-up imaging. It should be noted that, also in our retrospective study, toxicity levels could be underreported.

The ReRT risk score introduced by Niyazi et al. [20] was validated in our cohort. To our knowledge, this score has not been independently externally validated before. The calibration was good, shown by the corresponding results of the Cox regression and Kaplan–Meier estimators (mOS of the prognostic groups in our cohort: 14.6, 9.76, 5.32 months versus Niyazi's development cohort 14.2, 9.1 and 5.3 versus Niyazi's validation cohort 13.8, 8.8 and 3.8 months). The graphically evaluation of the Kaplan–Meier curves and the reported HRs showed good discrimination between the prognostic groups. However, in formal test, the discrimination was modest corresponding to the value mentioned by Niyazi et al. (c-index <0.7), which was not an issue specific to the validation process. Clearly this should be considered regarding the usefulness of the ReRT risk score in practice. Nevertheless, even a model that stratifies risk relatively weakly may be better than no model at all.

Limitations

A number of important limitations for our study needs to be considered. The retrospective study design is susceptible to bias and confounding. Including only the patients that were selected by tumor boards for ReRT introduced selection bias. For this reason, the results are only applicable to patients that are considered eligible for ReRT by a tumor board comparable to ours.

In addition, availability and accuracy of the medical record was suboptimal. A major drawback of this study is that quality of life and neurocognitive function could not be assessed and toxicity was difficult to extract. Estimation of KPS based on record keeping leads to less precision of this already subjective measurement. To increase accuracy, KPS was subdivided into categories. In 19 cases the diagnosis of recurrence was histopathologically confirmed. Other cases could be wrongly classified based on MRI, or even be inaccurately diagnosed as recurrence. Some potential predictors were not available for analysis in our database. We did not define central, in-field, marginal and out-field recurrences like Lee et al. [33] and we were unable to extract steroid baseline dose for all patients. These are both potential prognostic factors for OS [11,19]. Moreover, the sample size of patients with performed molecular or genomic screening tests was too small to include in multivariate analysis.

Thirdly, confounding by indication is introduced by the fact that treatments are preferentially prescribed to groups of patients based on their underlying risk profile. Unequally divided variables were added to the multivariate regression to correct for confounding. Still, undetected confounding could have occurred.

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Moreover, the small sample size may introduces the risk of overfitting and incorrect acceptance of the hypothesis of equal distribution of variables. Since the number of parameters in multivariate analysis exceeded the rule of 10 outcome events per predictor, these results should be interpreted with caution.

Multicenter studies are susceptible for heterogeneities in data collection and difference in treatment algorithms. To minimize heterogeneity in data collection, data were extracted in close consultation between the researchers to ensure the variables were extracted in the same way.

Conclusion

In conclusion, ReRT is still a promising strategy for treatment of recurrent glioma. We were not able to discern an optimal treatment regimen from CFRT, HFRT or SRT. No significant difference in OS was found between these dose-fractionation groups, mOS was 9.7 months overall after ReRT. Also no significant difference between the low toxicity rates was reported. Based on these results no recommendation can be made in favor of one of the regimens. Patient and tumor characteristics and patient burden should be considered in clinical practice, as was shown by validating Niyazi's ReRT score in our cohort.

Nevertheless, some promising results were obtained and it is worthwhile to pursue this approach to develop a better treatment decision tool. To achieve this, larger retrospective research in collaboration with more hospitals of the national platform is warranted to analyze the various treatment regimens in multivariate regression, perform subgroup analyses and investigate the toxicity outcome. Thereafter, prospective research is necessary to validate the developed tool and to assess patient relevant outcomes including quality of life.

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Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.10.034.

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