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Outcomes of Isocitrate Dehydrogenase Wild Type Glioblastoma after Re-irradiation

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ABSTRACT

Purpose: Glioblastomas (GBM) are the most common malignant primary brain tumors in adults and have a dismal prognosis. Patients frequently suffer from local tumor recurrences, with limited therapeutic options. Re-irradiation represents a possible intervention, but given the recent 5th edition of the World Health Organization classification of central nervous system tumors, studies in isocitrate dehydrogenase wild type (IDH-wt) cohorts undergoing a second course of radiotherapy remain limited. Herein, we sought to describe our institutional experience and outcomes after GBM IDH-wt re-irradiation.

Materials and Methods: GBM patients with confirmed IDH-wt status undergoing re-irradiation were included in this single-center, retrospective analysis.

Results: A total of 88 patients were analyzed. The median clinical and radiographic follow-up periods were 4.6 months and 4.4 months, respectively. Most patients had a Karnofsky performance status of at least 80% (n = 57). The median biologically effective dose and 2 Gy equivalent dose (EQD2) for re-irradiations, assuming an α/β ratio of 10 Gy for GBM, were 51.4 and 42.8 Gy, respectively. In total, 71 deaths were recorded. The median overall survival (OS) was 8.0 months. Multivariable Cox regression of OS revealed a positive influence of gross total resection vs. biopsy or no resection (hazard ratio: 0.43, p = 0.02). The median progression-free survival (PFS) was 5.9 months. The multivariable Cox regression for PFS did not detect any significant factors. No clear evidence of radiation necrosis was recorded during the available follow-up. However, only a minority (n = 4) of patients underwent surgery after re-irradiation, none showing histopathological proof of radiation necrosis.

Conclusion: The prognosis for recurrent IDH-wt GBM after re-irradiation is poor. Patients who are amenable and able to undergo re-resection may have a favorable OS. A second course of radiotherapy with a moderate cumulative EQD2 and small- to medium-sized planning target volumes appeared safe regarding the occurrence of radiation necrosis.

Introduction

Glioblastoma (GBM) represents the most common type of primary malignant brain tumor in adults and is associated with a dismal prognosis [1]. In non-elderly patients with good performance status, the standard of care typically comprises safe gross total resection, followed by radiation therapy (RT) and chemotherapy (CT) with temozolomide (TMZ) [2,3]. However, most patients with GBM experience a relapse within two years after their initial treatment. Recurrence usually occurs locally within the previously irradiated area [4,5]. Most patients have an overall survival (OS) of less than two years despite trimodal therapy [6]. There is no established gold standard of treatment after GBM recurrence or tumor progression [2]. Options for treatment include re-resection, re-irradiation, systemic treatment, or a combination of these approaches

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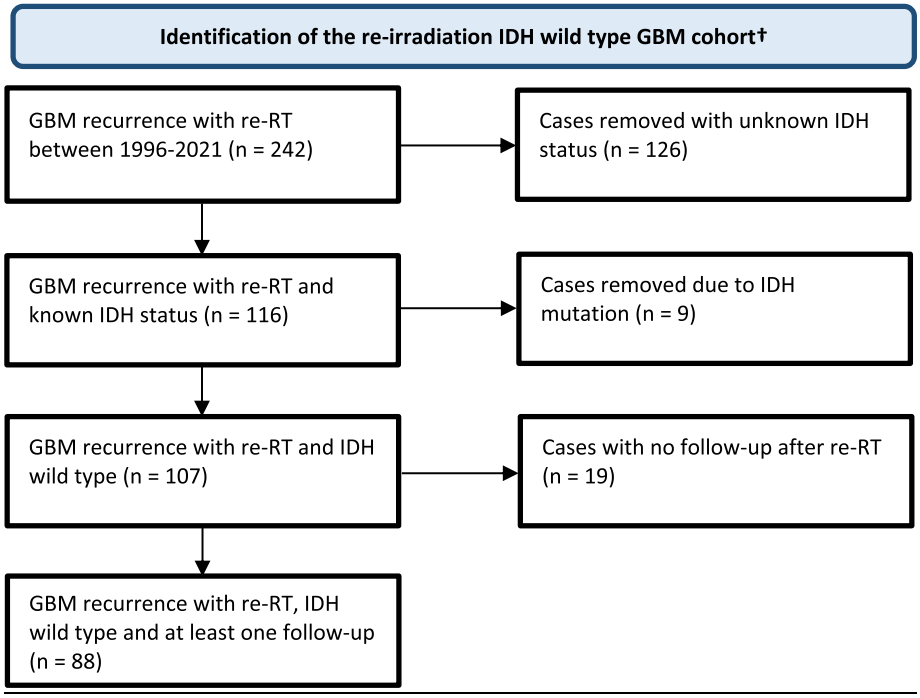
Table 1
Patient cohort flowchart.



IDH: isocitrate dehydrogenase, GBM: glioblastoma, re-RT: re-irradiation. †: Patients with a histopathologically confirmed GBM diagnosis were screened.

[7]. Current fields of research in GBM treatment include molecularly targeted therapies, immunotherapy, vaccines, nanoparticles, antibodies, tumor-treating fields (TTF), or modified radiation schedules, all of them potentially viable in the recurrent setting as well [5].

Historically, the risk of severe side effects from exceeding the dose tolerance of healthy brain tissue has made radiation oncologists hesitant to consider re-irradiation with high doses. However, the tolerance doses and constraints of healthy brain tissue remain a subject of discussion and are not well established [8,9]. In patients with favorable clinical criteria and a focal relapse, many clinicians consider a second local treatment, such as re-resection, re-irradiation, or both with and without systemic therapy [4]. There is a lack of consensus among experts on the ideal way to use RT to treat recurrent GBM and how to stratify patients [4]. A survey of radiation oncologists found significant variation in their approaches, reflecting the limited high-quality data available for making treatment decisions [10]. Many questions remain unanswered, including which patients are most likely to benefit from additional RT, what dose and fractionation should be used, how to define the target volume, and which imaging technique and sequences are best for planning [4,8].

With the recent update of the World Health Organization (WHO) classification of tumors of the central nervous system, a significant and notable change has been made in the definition of GBM [11]. GBM now refers to isocitrate dehydrogenase (IDH) wild type (IDH-wt) astrocytoma, grade 4 [11]. This substantial change significantly impairs the comparability, outcome assessment, and interpretation of recent studies, given the usual inclusion of IDH-wt and IDH-mutant (IDH-mt) GBM [12]. With the lack of studies on re-irradiation in clearly defined IDH-wt GBM cohorts, we sought to analyze our institutional experience and provide outcomes concerning OS and progression-free survival (PFS).

Materials and methods

Patients with a histopathologically confirmed GBM diagnosis at our institution were screened. Inclusion criteria of this single-center, retrospective cohort study were: patients with recurrent IDH-wt GBM, treated between 1996 and 2021, at least one clinical follow-up, age $\geq$ 18 years at first diagnosis, and having received any type of re-irradiation, with the exception of patients receiving stereotactic radiosurgery (SRS). Re-irradiation was defined as a new course of RT with an overlap of the previously irradiated volume with or without concern of toxicity as defined by the ESTRO-EORTC consensus [13]. IDH status could have been confirmed at initial diagnosis or recurrence. PFS was determined from the first day of re-irradiation to death or radiographic progression assessed by magnetic resonance imaging (MRI). A board-certified neuroradiologist assessed tumor progression. Gross tumor volume delineation regularly included the newly diagnosed contrast-enhancing regions on T1-weighted MRI. The new resection cavity was also included in patients undergoing surgical resection. Margins for the clinical target volume (CTV) as well as selection of the total dose and number of fractions were at the discretion of the managing physician with respect to previous doses to organs at risk. Typically, margins to create the CTV were chosen to be between 0 and 10 mm. An additional margin for the technical setup was added to generate the planning target volume (PTV). OS was calculated from the first day of re-irradiation to the date of death. Patients were censored at the last available follow-up if no death or progression was observed. Follow-up regularly included clinical and radiological evaluation every 3 months or depending on the patient's performance status. Radiographic follow-up was calculated from the first day of re-irradiation until the last available MRI. Clinical follow-up was the period between the first day of re-irradiation and the last clinical visit. The primary outcome was OS, with PFS as a secondary outcome, both calculated according to the Kaplan–Meier estimate. PFS and OS were correlated with patient-, tumor- and treatment-related variables via multivariable Cox regression. Variable selection was done *a priori* and based on previously known factors, besides initial O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status, given the considerable overlap of patients with MGMT promoter-methylated tumors and TMZ-based CT (collinearity). The proportional hazards assumption was tested with Schoenfeld residuals. Missing data were not replaced by imputation methods. The 2 Gy equivalent dose (EQD2) and biologically effective dose (BED) were calculated as

Table 2
Patient and treatment characteristics.

Number of patients			88	
Sex (male/female)	32		56	
	Median	**Mean (SD)**	**IQR**	**Range**
Age at first diagnosis (years)	57.2	57.5 (10.4)	50.2 – 64.9	35.4 – 78.9
Time from first diagnosis to re-RT (months)	16.5	19.1 (10.6)	11.8 – 20.9	2.3 – 60.0
Age at re-RT (years)	58.7	59.0 (10.4)	51.0 – 66.6	36.6 – 79.4
Radiographic follow-up (months)	4.4	6.5 (7.1)	2.3 – 7.8	0.0 – 33.0
Clinical follow-up (months)	4.6	7.2 (6.9)	3.2 – 8.6	0.1 – 33.1
EQD2, 1. RT (Gy)[a]	60	58.4 (7.9)	57.2 – 60.0	16.0 – 67.1
BED, 1. RT (Gy)[a]	72.0	70.0 (9.5)	68.6 – 72.0	19.2 – 80.5
EQD2, re-RT (Gy)	42.8	46.7 (10.3)	42.1 – 57.2	6.1 – 60.0
BED, re-RT (Gy)	51.4	56.1 (12.4)	50.6 – 68.6	7.4 – 72.0
Total EQD2 (Gy)[a]	107.6	105.0 (13.6)	99.0 – 114.4	66.0 – 127.1
Total BED (Gy)[a]	129.1	126.0 (16.3)	118.8 – 137.3	79.2 – 152.5
Number of fractions, re-RT	15	–	13 – 36	4 – 37
Planning target volume re-RT (cc)[b]	98.0	114.7 (97.6)	42.5 – 145.5	7.9 – 584.4
KPS (%)[b]	80	–	70 – 90	40 – 100
MGMT promoter methylation[b]	Yes	No		
Number of patients	40	45		
Chemotherapy	TMZ	CCNU	Other	None
Number of patients	50	9	12	17
Resection status before re-RT[a]	GTR	STR	Biopsy	No surgery
Number of patients	27	13	1	45
Number of observed progressions	32			
Number of observed deaths	71			

SD: standard deviation, IQR: interquartile range, re-RT: re-irradiation, EQD2: 2 Gy equivalent dose, BED: biologically effective dose, RT: radiotherapy, cc: cubic centimeters, KPS: Karnofsky performance status, IDH: Isocitrate dehydrogenase, MGMT: O^6-methylguanine-DNA methyltransferase, TMZ: temozolomide, CCNU: lomustine, GTR: gross total resection, STR: subtotal resection.

[a] Not available for 2 patients.

[b] Not available for 3 patients.

previously described, assuming an α/β ratio of 10 Gy for GBM [14,15]. The statistical significance was defined as a p-value of ≤ 0.05. Statistical analysis was performed using STATA MP 17.0 (StataCorp, College Station, TX, USA). Figures were created with STATA MP 17.0 and GraphPad Prism 8.01 (GraphPad Software, San Diego, CA, USA). The study was approved by the local institutional review board (EA4/171/21).

Results

Two hundred forty-two patients with recurrent GBM treated with re-irradiation between 1996 and 2021 were identified. After applying the inclusion criteria, 88 eligible patients were included in this study (Table 1). Patient characteristics are shown in Table 2. The median age at first diagnosis was 57.2 years, and our cohort consisted of 32 men and 56 women. All patients had confirmed IDH-wt GBM recurrence. The MGMT promoter was methylated in 45.4% of cases (n = 40) and unmethylated in 51.1% (n = 45). The median clinical and radiographic follow-up times were 4.6 months and 4.4 months, respectively. Nine patients with a median clinical follow-up of 3.4 months were censored. All re-irradiations were conducted between March 2011 and December 2021.

Patients at initial diagnosis received radiotherapy mostly with 30 × 2 Gy (n = 39) and 37 × 1.6 Gy twice daily (n = 20). One patient discontinued initial radiotherapy after a total dose of 16 Gy due to a worsening performance status. After a median time of 16.5 months, patients started re-irradiation for GBM recurrence. The median EQD2 and BED for re-irradiation, using an α/β ratio of 10 Gy, were 42.8 Gy and 51.4 Gy, respectively (Table 2, Fig. 1). Before, 40 patients (45.4%) underwent gross total- or subtotal resection (GTR/STR). The median Karnofsky performance status (KPS) at the start of re-irradiation was 80%. Most patients had a KPS of at least 80% (n = 57), with only eight patients having 60% or less. The number of patients with a KPS of ≥ 90% and ≤ 70% were 37 and 28, respectively.

Most patients received additional CT with TMZ only (56.8%). The second most used single CT was CCNU (lomustine) (10.2%). Twelve patients received various combinations of TMZ, CCNU, bevacizumab, procarbazine, vincristine, and regorafenib. The majority of patients with MGMT promoter methylated tumors received CT (33/40 patients, 82.5%). Re-irradiation fractionation schemes were heterogeneous and primarily consisted of 37 × 1.6 Gy twice daily (n = 21), 13 × 3.0 Gy (n = 18), and 10 × 3.4 Gy (n = 10). The median PTV was 98.0 cc.

Median OS was 8.0 months (95% confidence interval (CI): 6.9 – 9.6 months). In total, 71 deaths were recorded. The 6-, 12-, 18- and 24-months OS rates were 72.0%, 32.7%, 18.5%, and 9.2%, respectively (Fig. 2, Table 3). Multivariable Cox regression of OS revealed a positive influence of GTR vs. biopsy or no resection on OS (hazard ratio (HR): 0.43, p = 0.02, Table 4). Median OS with GTR or STR was markedly longer than in patients without surgical resection or biopsy only (10.3

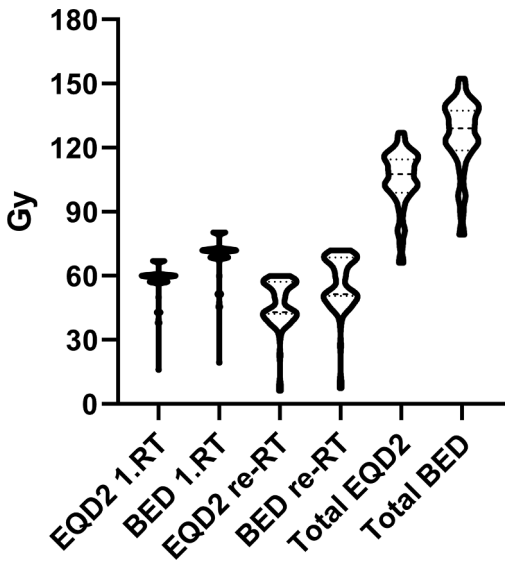


Fig. 1. Violin plot of the EQD2 and BED in this cohort. EQD2: 2 Gy equivalent dose, RT: radiotherapy, re-RT: re-irradiation, BED: biologically effective dose.

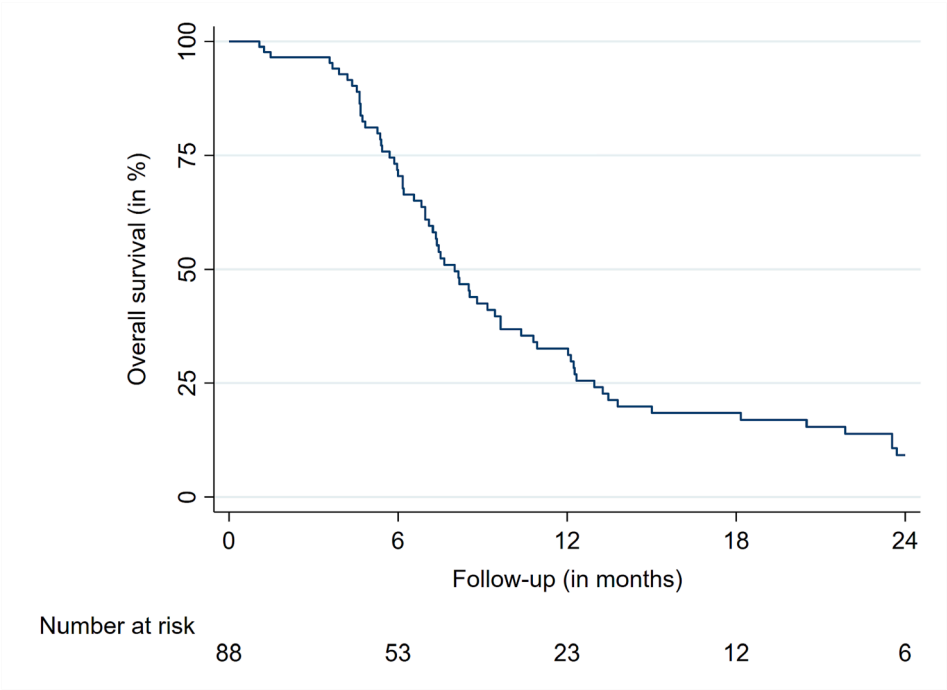


Fig. 2. Overall survival after re-irradiation.

Table 3
Overall survival and progression-free survival after 6, 12, 18, and 24 months.

	OS				PFS			
Time (months)	6	12	18	24	6	12	18	24
Survival probability (%)	72.0	32.7	18.5	9.2	49.3	15.7	6.5	3.9
Confidence interval (95%)	60.6 – 80.6	22.2 – 43.6	10.5 – 28.2	3.8 –17.5	38.1 – 59.6	8.7 – 24.6	2.4 – 13.5	1.0 – 10.0

OS: overall survival, PFS: progression-free survival.

Table 4
Multivariable Cox proportional hazards model for OS.

Variable	Multivariable Cox proportional hazards model		
	Hazard ratio	Confidence interval (95%)	p-value
KPS $\geq$ 80%			0.71
No	Reference		
Yes	1.15	0.53 – 2.50	
Age (years)	0.99	0.97 – 1.02	0.81
Resection			0.02
No surgery or biopsy	Reference		
STR	0.47	0.20 – 1.12	
GTR	0.43	0.20 – 0.91	
Chemotherapy			0.74
No	Reference		
Yes	1.13	0.53 – 2.42	
Time from first diagnosis to start of re-RT (months)	0.98	0.95 – 1.00	0.21
PTV (cc)	1.00	1.00 – 1.00	0.01
EQD2 re-RT (Gy)	0.99	0.96 – 1.02	0.53

KPS: Karnofsky performance status, STR: subtotal resection, GTR: gross total resection, re-RT: re-irradiation, PTV: planning target volume, cc: cubic centimeters, EQD2: 2 Gy equivalent dose.

vs. 6.9 months, Fig. 3). The PTV was found to have a significant association in the Cox regression analysis. However, the HR was low given the measurement per cc (HR: 1.0034, p = 0.01).

Median PFS was 5.9 months (95% CI: 4.6 – 6.9 months) for the entire cohort. Thirty-two tumor progressions were observed during the radiographic follow-up. The 6-, 12-, 18- and 24-months PFS rates were 49.3%, 15.7%, 6.5%, and 3.9%, respectively (Fig. 4, Table 3). Multivariable Cox regression revealed no significant factors (Supplementary File 1).

The most common adverse events during and after re-irradiation were headaches (27.3%), nausea (25.0%), vertigo (23.9%), and fatigue (17.0%). Seizures were noted in six patients (6.8%). Five patients did not complete the initially planned re-irradiation due to adverse events or personal preferences. For patients with available MRI after completion of re-irradiation (n = 83, 94.3%), no suspicion for radionecrosis was reported. Four patients underwent another surgical resection after re-irradiation without any histopathological evidence of radiation necrosis.

Discussion

Data on the role of re-irradiation in pure IDH-wt GBM cohorts since the 5th edition of the WHO classification for tumors of the central nervous system remain scarce [7,12]. Despite the heterogeneity concerning the IDH mutation status in previous studies, our observed OS and PFS outcomes emphasize the dismal prognosis of recurrent GBM even after re-irradiation. The median OS of 8 months in this series appears comparable to other studies. For example, NRG Oncology/RTOG1205, a randomized controlled trial for re-irradiation in recurrent GBM investigating the combination of RT and bevacizumab in this setting, showed median OS times of approximately 10 months in both trial arms [16]. Notably, IDH status was not reported, which may have led to the inclusion of more favorable IDH-mutant tumors, explaining the prolonged median OS compared to this cohort. Another analysis reported treatment outcomes in IDH-wt tumors after photon and carbon ion re-

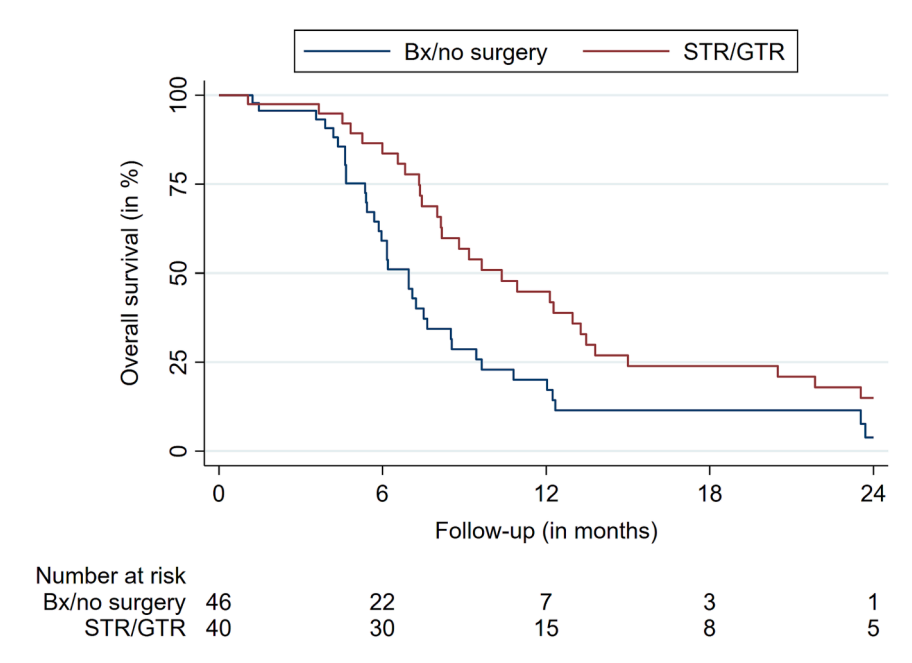


Fig. 3. Overall survival after re-irradiation, stratified by surgical status. Bx: biopsy, STR: subtotal resection, GTR: gross total resection.

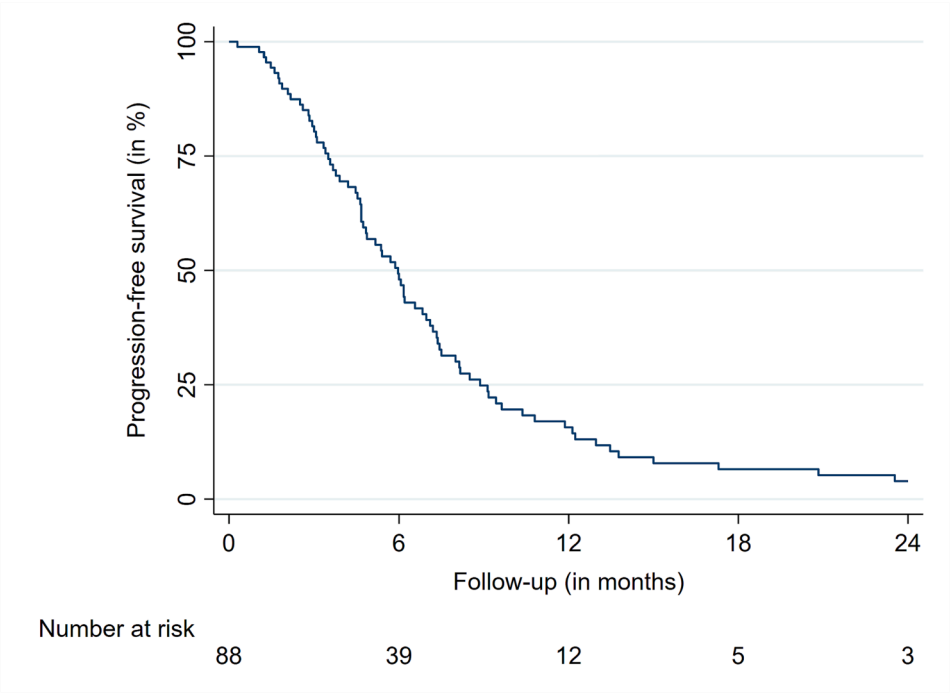


Fig. 4. Progression-free survival after re-irradiation.

irradiation [17]. Favorable results, i.e., longer OS, were observed for carbon ion treatments, but applied doses were higher compared to photon irradiations, impeding further conclusions. Other analyses found similar OS results utilizing proton therapy [18,19]. Outcomes after photon re-irradiation also demonstrated comparable median OS rates to those observed herein [7,8,20]. Again, heterogeneity concerning the IDH mutation status may account for a significant proportion of the minor to moderate differences besides other factors, including varying KPS, the possibility of re-resection, time to re-irradiation, tumor size, MGMT promoter methylation status, and other comorbidities.

The multivariable analysis revealed a successful re-resection, i.e., GTR, as a favorable prognostic factor for OS. Whereas STR did not formally decrease the risk of death, a clear effect might be present in larger cohorts. However, a potential survival advantage is not the only factor to consider when managing patients who are amenable to re-resection. The quality of life of affected patients with otherwise good performance status may be improved by reducing the tumor burden even in the case of STR. Finally, a reduced tumor mass could decrease the PTV which makes a re-irradiation safer. Thus, the surgical management of patients should be carefully assessed.

Another well-established patient characteristic, the KPS, did not influence the OS [3,20]. While this is surprising at first glance, the overall favorable patient characteristics and KPS distribution among our cohort are proper explanations for this observation. The vast majority of the GBM patients receiving a re-irradiation herein had a KPS of at least 70% before the start of RT (n = 77, 87.5%). Discrimination within a group of patients with such homogenous performance status would only be feasible with a significantly larger cohort. Therefore, we decided to compare patients with excellent, i.e., ≥ 80%, and good to moderate, i.e., ≤ 70%, KPS.

As expected, larger PTV, i.e., higher tumor burden at recurrence, was associated with a worse outcome. Besides, the use of CT, which was predominantly based on TMZ in MGMT promoter methylated GBM, did not formally show a benefit despite graphical separation of the OS curves (Supplementary File 2). Therefore, the inclusion of MGMT promoter methylation status as an own variable in the Cox model was waived. Survival curves of patients with methylated and non-methylated MGMT promoters did not show clear differences as well (Supplementary File 3). However, the small sample sizes and imbalances of these subgroups may have hindered the detection of meaningful effects. Given the regular use of TMZ during first-line treatment, however, the success of a re-challenge in a progressive tumor might be mixed. This is highlighted by the genetic and microenvironmental changes in progressing tumors which also show a distinct upregulation of neuronal signaling and hypermutational status, increasing recurrent tumor aggressiveness and, ultimately, treatment resistance [21]. In conclusion, validated prognostic factors in IDH-wt GBM after re-irradiation remain an active area of investigation [4]. Ongoing trials like the BRIOChe trial (EudraCT Number: 2019–004053-91), investigating the role of re-irradiation versus CT in GBM, are crucial to improve patient outcomes in the future. Other trials are investigating the experimental combination of re-irradiation with immunotherapy or poly(adenosine-5′-diphosphate-ribose) polymerase inhibitors (NCT05131711, NCT05666349). Finally, completed trials may be re-analyzed for outcomes of IDH-wt patients to provide more insights and generate further hypotheses.

Another critical topic concerning the re-irradiation of high-grade gliomas is the potential risk of radiation necrosis [4,8,9]. Validated brain tissue constraints for re-irradiations remain scarce [8,22]. The available data suggest a relatively low risk of radiation necrosis if the cumulative EQD2 is between 100 and 110 Gy [8,22]. Total EQD2 doses above may lead to a significant danger, especially if the re-irradiated volume is large [8]. This risk is particularly pronounced when SRS or fractionated stereotactic radiotherapy is applied, given the underlying uncertainty of the linear quadratic model to adequately depict the radiobiological consequences of high doses per fraction and the observed rates of radiation necrosis [8,23]. Herein, the median and mean total EQD2 doses were 107.6 and 105.0 Gy, respectively. For patients with radiographic follow-up, we did not observe cases suggestive of radiation necrosis. While patients regularly suffered from disease progression even shortly after re-irradiation and in the absence of comprehensive histopathological information, it cannot be formally ruled out that a proportion of the patients developed radiation necrosis. Nevertheless, three factors may lead us to the conclusion of a relatively low rate of radionecrosis in this cohort. First, the majority of applied total EQD2 doses were below 120 Gy (80/86 patients, 93.0%), a dose that can be considered safe in the light of conventionally fractionated RT [8]. Second, the majority of PTV was small to medium, with more than 70% being below 150 cc. As volumetric considerations may be especially relevant for the risk of radiation necrosis, re-irradiations of small volumes appear justifiable [8,24]. Finally, we did not include any re-irradiations with SRS, which are known for an elevated risk of radiation necrosis apart from the cumulative EQD2 and the underlying radiobiological reasons. The lack of prospectively validated data on the occurrence of radiation necrosis and the roles of its determining factors remain significant barriers to advancing the field of re-irradiation in GBM. Our analysis complements the current evidence that re-irradiations with moderate cumulative EQD2, i.e., up to 120 Gy, may be appropriate in selected patients with small- to medium-sized PTV.

Apart from the limitations intrinsic to the retrospective design, our study had several limitations. First, the included patients received varying fractionation schemes as well as systemic treatments and comprised a rather heterogeneous group. This hinders the identification of prognostic factors but represents the daily clinical routine and emphasizes the lack of consensus guidelines for managing recurrent GBM. In addition, the analysis of acute and chronic toxicity is affected by the limited data as patients regularly transitioned to best supportive care soon after re-irradiation. The diagnosis of radionecrosis, an essential point of interest after re-irradiation, was hampered by the lack of serial follow-up imaging and comprehensive tissue analysis, given the dismal prognosis and short OS. Assessment and differentiation of radionecrosis remain neuro-oncological challenges, especially when only contrast-enhanced MRI is available [9].

Conclusion

The prognosis for recurrent IDH-wt GBM after re-irradiation is poor. Patients who are amenable and able to undergo re-resection may have a favorable OS. The toxicity of re-irradiation appears manageable for moderate doses and small- to medium-sized PTV. Further research in IDH-wt cohorts is warranted to improve patient outcomes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2023.100653.

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