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# Reirradiation of gliomas with hypofractionated stereotactic radiotherapy: efficacy and tolerance analysis at a single center

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## ABSTRACT

**Background:** Recurrent high-grade gliomas present a therapeutic challenge. Repeat surgery, re-irradiation, and systemic therapy have been explored, with re-irradiation requiring precise tumor relapse delineation and advanced dosimetric techniques. This study aims to evaluate the effectiveness and tolerability of re-irradiation using Hypofractionated Stereotactic Radiation (HFSRT) schedules.

**Materials and methods:** In a retrospective analysis from 2011 to 2021, 52 adult patients with recurrent high-grade gliomas were examined, including 42.3% with glioblastoma, 32.5% with grade 3 gliomas, and 25% with grade 2 gliomas as initial diagnosis. All received prior radiotherapy at doses ranging from 54–60 Gy, with a median time to tumor relapse of 19.8 months. Salvage surgery was performed in 42.3% of cases, with a median interval of 22.45 months between radiation courses. Re-irradiation doses were 30 Gy in 5 fractions for 54% and 40 Gy in 10 fractions for 46%. Concurrent systemic treatments included temozolomide (30.8%), nevacizumab (27%), or none (35%).

**Results:** In-field and out-field tumor progression occurred in 65.4% and 25% of patients, with median times to local and distant progression of 5.17 and 4.57 months. Median overall survival (OS) from re-irradiation was 12 months. Univariate analysis showed a trend favoring 30 Gy in 5 fractions for disease progression-free survival (DPFS). Treatment was generally well-tolerated, with only 5.7% experiencing acute Grade-3 toxicity, and symptomatic radionecrosis occurred in 2 patients.

**Conclusion:** Re-irradiation using HFSRT for recurrent high-grade gliomas is viable and well-tolerated, demonstrating survival rates comparable to existing literature. These findings underscore the potential of HFSRT in managing recurrent high-grade gliomas.

**Key words:** reirradiation; high grade gliomas; glioblastoma; hypofractionation; stereotactic radiation

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## Introduction

Primary brain tumors account for 1.5% of all cancers, with gliomas representing 26% of primary central nervous system (CNS) tumors [1]. The standardized incidence of CNS gliomas in Europe is 4.8 per 100,000 per year, and they are more prevalent in men [2].

Traditionally, gliomas have been classified as low-grade or high-grade tumors, with high-grade glioblastoma being the most common malignant brain tumor in adults. The 2016 World Health

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Organization (WHO) classification emphasizes the importance of molecular profiling as a prognostic factor, with updates continuing until 2021 [3, 4].

The treatment of gliomas involves surgery, radiotherapy, and chemotherapy. Despite these therapeutic approaches, the rate of relapse and local progression remains high, reaching 40% for low-grade tumors and up to 90% for high-grade gliomas. The standard treatment for glioblastoma multiforme includes surgery followed by external beam radiation therapy (RT) with concomitant and maintenance temozolomide, resulting in a reported median survival time of 14.6 months and a 2-year survival rate of 26.5%, respectively [5, 6].

Treatment options for recurrent high-grade gliomas are not well established and present a significant therapeutic challenge. Options include repeated surgery, re-irradiation, local chemotherapy, systemic therapy with chemotherapy, or molecular antibodies [7]. Radiotherapy for recurrent high-grade gliomas is particularly challenging, as the majority of these tumors have already been treated with radiation in standard protocols. Accurate magnetic resonance imaging (MRI)-based delineation of tumor relapse and advanced dosimetric techniques are crucial for reirradiation of high-grade gliomas [8]. Hypofractionated stereotactic radiation therapy (HFSRT) techniques allow the delivery of high radiation doses with stereotactic precision, maximizing the biological effect of high doses in a few fractions while protecting surrounding healthy tissue.

The decision to undergo salvage re-irradiation must be individualized, considering factors such as the patient's age, general and neurological condition, lesion location and size, previous radiation treatment and dose, relapse pattern, histological grade, and the time between initial radiotherapy and re-irradiation.

In this study, we present our experience using HFSRT for the radical treatment of locally recurrent CNS gliomas that have been previously irradiated. We also provide a review of existing experiences in the field.

## Materials and methods

### Patients and data acquisition

After obtaining approval from the Local Ethics and Clinical Research Committee, we conducted a retrospective review of adult patients diagnosed with locally recurrent CNS glioma who underwent HFSRT re-irradiation at our institution between 2011 and 2021. The objectives of this study were to evaluate the efficacy of re-irradiation with HFSRT and the tolerance of both radiation schemes in this patient population.

All treatment decisions were made by a multidisciplinary tumor board consisting of neuroradiologists, medical and radiation oncologists, pathologists, and neurosurgeons. Patient selection was based on performance status [at least 0–2 according to Eastern Cooperative Oncology Group (ECOG)] and a minimum interval of six months from the previous radiotherapy.

Complete characteristics of included patients are detailed in Table 1.

All patients included in our analysis had a confirmed high-grade glioma relapse, either through biopsy or MRI findings. The diagnosis

**Table 1.** Patients' characteristics at diagnosis

| | N | % |
|---|---|---|
| **Sex** | | |
| Female | 20 | 61.5 |
| Male | 32 | 38.5 |
| **Histology at diagnosis** | | |
| GII | 13 | 25 |
| GIII | 17 | 32.7 |
| GIV | 22 | 42.3 |
| **Extension of surgery** | | |
| R0 | 15 | 28.8 |
| R1 | 29 | 55,8 |
| Biopsy | 8 | 15.4 |
| **IDH1** | | |
| Mutated | 3 | 5.8 |
| Wild type | 14 | 26.9 |
| NA | 35 | 67.3 |
| **IDH2** | | |
| Mutated | 1 | 1.9 |
| WT | 14 | 26.9 |
| NA | 37 | 71.2 |
| **MGMT** | | |
| Metilated | 7 | 13.5 |
| Non metilated | 11 | 21.2 |
| NA | 34 | 65.4 |

**Table 1.** Patients' characteristics at diagnosis

| | N | % |
|---|---|---|
| **1p19q** | | |
| Codeletion | 7 | 13.4 |
| No codeletion | 8 | 15.4 |
| NA | 37 | 71.2 |
| **RT dose (first treatment)** | | |
| 60 Gy | 44 | 84.6 |
| 54 Gy | 8 | 15.4 |
| **Systemic therapy** | | |
| TMZ | 45 | 88.5 |
| PVC | 2 | 3.8 |
| TMZ + Bevacizumab | 1 | 1.9 |
| No QT | 3 | 5.8 |

R0 — complete resection; R1 — incomplete resection or biopsy; NA — not available; WT — wild type; G — grade; PVC — procarbazine, lomustine and vincristine; TMZ — temozolamide

of high-grade recurrence in all patients was based on brain MRI with gadolinium, including volumetric T1-weighted, contrast-enhanced T2 Flair, perfusion, and spectroscopy sequences.

Patients included in the study may have initially been diagnosed with either high-grade or low-grade gliomas and had previously received radiotherapy within the range of 54–60 Gy using conventional fractionation.

## Treatment procedure

Radiotherapy simulation-CT was performed using an individualized thermoplastic mask (BrainLAB AG, Munich, Germany) specifically designed for radiosurgery and stereotactic fractionated radiotherapy, ensuring daily immobilization and precise repositioning. Computed tomography (CT) axial images were acquired at 1 mm intervals throughout the brain using a helical scanner. Additionally, a three Tesla MRI was performed for each patient, including volumetric, contrast-enhanced T1, and T2 Flair sequences, which were essential for treatment planning purposes.

CT and MRI images were first registered and subsequently fused using a rigid fusion technique, as depicted in Figure 3.

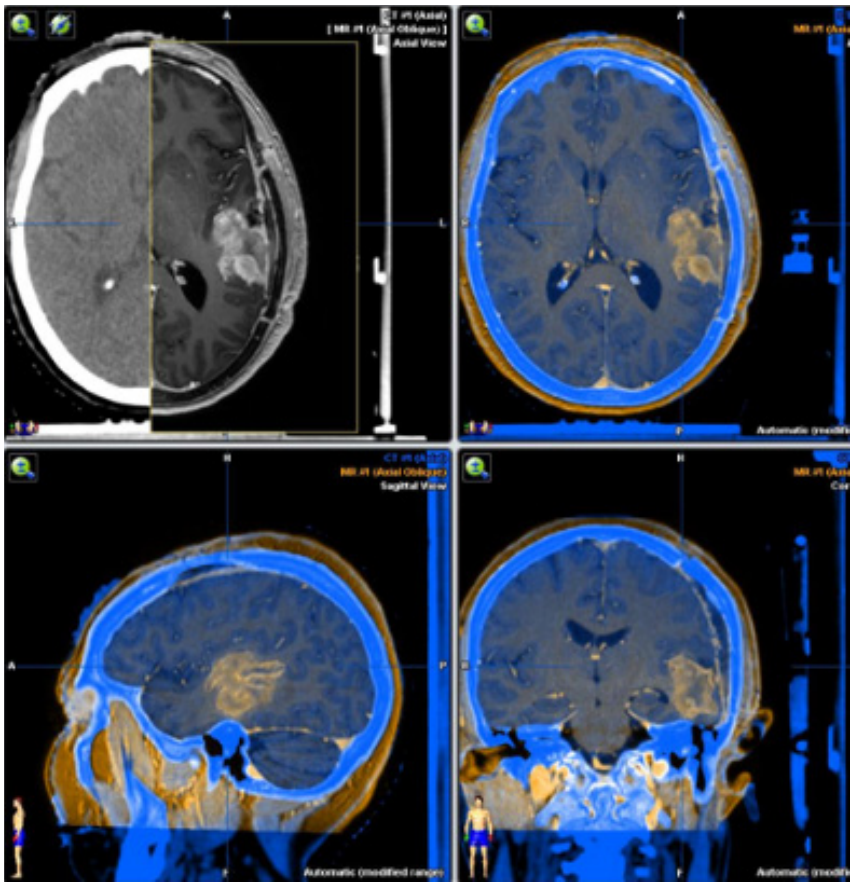

**Figure 3.** Computed tomography-magnetic resonance imaging (CT-MRI). Registration and fusion

**Table 2.** Dose constraints for organ at risk (OAR)

| Organ at risk | 30 Gy in 5 fractions | 40 Gy in 10 fractions |
|---|---|---|
| Brainsterm | Max dose 35 Gy<br>V18.7 < 60% | Max dose 44 Gy<br>V41.80 < 30%<br>V23 < 60% |
| Chiasm | Max dose 28 Gy | Max dose 35.5–37.7 Gy |
| Optic nerves | Max dose 28 Gy | Max dose 35.5–37.7 Gy |
| Eyes | Max dose 30 Gy<br>Average dose 21Gy | Max dose 38 Gy<br>Average dose 26 Gy |
| Lens | Max dose 5Gy | Max dose 6 Gy |
| Healthy brain tissue | V20 < 20 cc | Dosis 40 Gy < 33% |

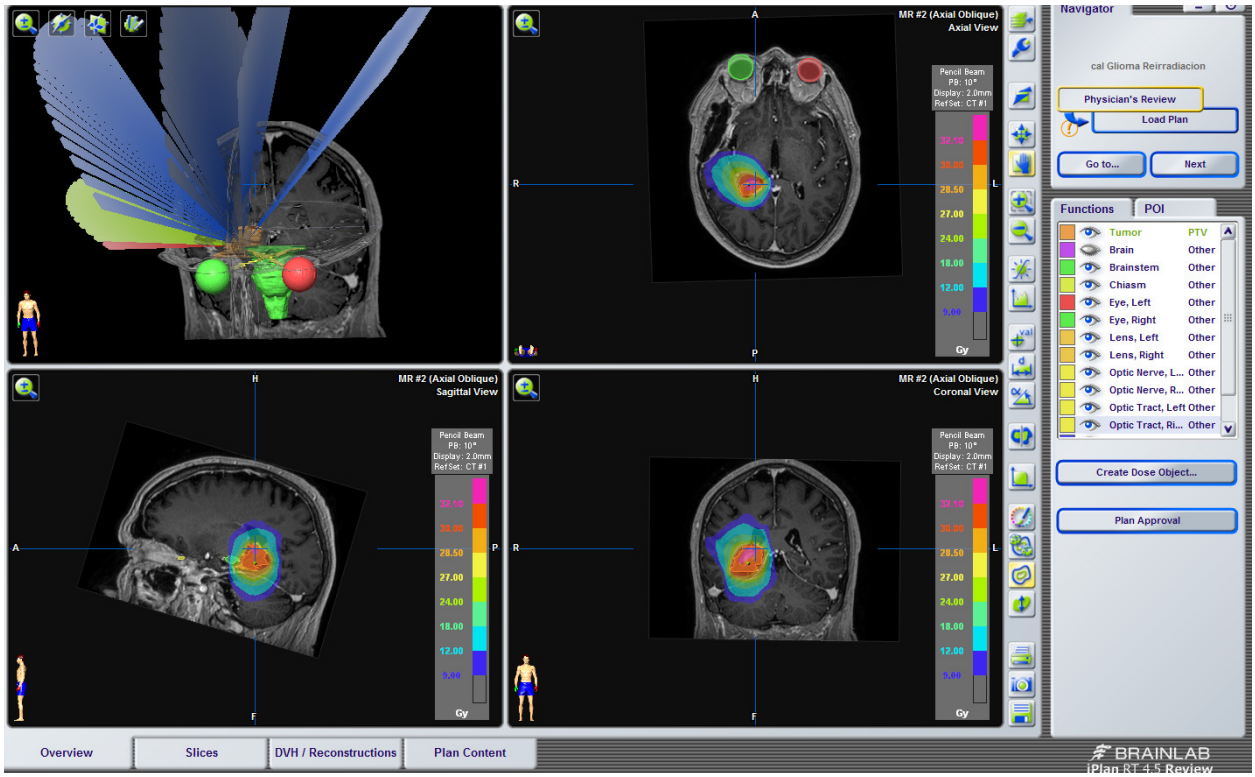


**Figure 4.** Treatment planning

Volumes of interest were delineated using iPlan (Brainlab AG, Munich, Germany) or RayStation (RaySearch Laboratories, Stockholm, Sweden) software. Target volumes and organs at risk (OARs) were delineated according to international recommendations [9]. Delineation was performed on T1-weighted gadolinium-enhanced MR sequences registered with the simulation-CT images.

The gross tumor volume (GTV) encompassed the surgical cavity and/or all macroscopic tumor recurrence. T2 Flair enhancement resulting from edema, post-treatment changes, or suspected disease was not routinely included in the clinical target volume (CTV), but was considered in specific cases. The CTV was then expanded isotropically by 3 mm to create the planning target volume (PTV).

OARs included the brainstem, optic chiasm, optic nerves, ocular globes, lens, upper spinal cord, and brain. Dose constraints for the OARs are detailed in Table 2.

Two hypofractionated stereotactic radiation therapy (HFSRT) schedules were administered in this study: 40 Gy in 10 fractions over 2 weeks and 30 Gy in 5 fractions over one week. The se-

lection of the specific schedule was determined by the treating physician, taking into consideration various clinical factors and individual patient characteristics.

To compare treatments administered with different doses and fractions, the concept of biologically effective dose (BED) was developed based on the linear-quadratic formalism. The BED is calculated using the formula:

$$BED = n \times d \times [1 + d / (\alpha / \beta)]$$

where n represents the number of fractions, d is the fraction size of the applied regime, and α/β is the ratio of radiation fractionation sensitivity, assumed to be 10 Gy for high-grade gliomas. For the 10 fractions of 4 Gy schedule, the corresponding BED10Gy value is 56 Gy, while for the 5 fractions of 6 Gy schedule, the BED10Gy value is 48 Gy.

The specific HFSRT schedule was chosen based on these BED calculations, taking into account the desired biological effect, treatment efficacy, and potential side effects in the context of each patient's individual circumstances.

Dosimetry was performed using two different planning systems: iPlan (Brainlab AG, Munich, Germany) based on the Monte Carlo algorithm (XVMC), and RayStation (RaySearch Laboratories, Stockholm, Sweden) with dose calculation based on the collapsed cone algorithm. Highly conformal techniques, such as volumetric modulated arc therapy (VMAT) or intensity-modulated radiation therapy (IMRT), were employed for treatment planning to ensure adequate coverage and adherence to constraints. A treatment plan was considered acceptable if at least 90% of the target volume received the prescribed dose.

Radiation treatment was delivered using either a Classic Novalis (Brainlab AG, Munich, Germany) system with a micro-MLC (3 mm leaf width) and a nominal energy of 6 MV WFF, or a VERSA HD (Elekta AB, Stockholm, Sweden) system with an Agility MLC (5 mm leaf width) and a 6 MV FFF beam energy. Patients were treated five days per week with inter- and intrafraction IGRT (image-guided radiation therapy) verification using stereoscopic X-Ray images from the Exac-Trac System® (Brainlab AG, Munich, Germany) for the Novalis unit or kV-cone-beam CT (kV-CBCT) for the VERSA HD unit.

Concomitant systemic treatments, including temozolomide, bevacizumab, Procarbazine, Lomustine, or other agents, were selected by the medical oncologist.

## Treatment evaluation

During radiation treatment, patients were evaluated for tolerance on a weekly basis. Four weeks after the completion of treatment, and subsequently every 2–3 months until progression, death, or lost to follow-up, patients underwent an MRI scan for evaluation. Follow-up was measured from the end of re-irradiation to the date of the last evaluation.

Statistical analysis was performed using SPSS, version 20.0 (IBM Corp., Armonk, NY). Response to the first and second radiation course was assessed based on the RANO classification published in 2010 [10]. which categorizes response into complete response, partial response, stable disease, and progression based on imaging (MRI) and clinical features. Acute and late complications were scored according to the Radiation Therapy Oncology Group (RTOG)/EORTC Common toxicity criteria [11]. Acute toxicity was defined as adverse effects registered in patients from the first day to 3 months after the end of EBRT, while late toxicity was defined as adverse effects directly attributable to EBRT observed from 3 months to the date of the last follow-up. Only side effects attributable to the local treatments applied were recorded in the medical history.

Recurrences were classified as local or in-field and distant or out-of-field, always referring to intracranial recurrences. Local recurrence-free survival (LRFS) was calculated as the time from re-irradiation to a new in-field local recurrence confirmed by MRI imaging. Distant recurrence-free survival (DRFS) was estimated at the time of the first intracranial relapse outside the re-irradiated area confirmed by MRI imaging. Progression-free survival (PFS) was defined as the time interval between the end of re-irradiation and any tumor progression, while overall survival (OS) was calculated as the time between diagnosis and the date of death or last follow-up. Patients who died from intercurrent disease without evidence of tumor were censored at the date of death. Actuarial LRFS, PFS, and OS were determined using the Kaplan-Meier method, and survival curves were compared using

the log-rank test. Differences between groups were assessed using Pearson's chi-square test. A p-value of <0.05 was considered statistically significant.

## Results

### Clinical outcomes

Between 2011 and 2021, a total of 52 consecutive patients (32 males, 61%, and 20 females, 39%) with a median age of 55 years (range 22–76) and a diagnosis of recurrent high-grade gliomas underwent re-irradiation at our institution and were included in the analysis.

Regarding the primary diagnosis, 22 patients (42.3%) had glioblastoma, 15 patients (28.8%) had grade 3 astrocytoma, 7 patients (13.4%) had grade 2 oligoastrocytoma, 6 patients (11.5%) had grade 2 astrocytoma, and 2 patients (3.8%) had grade 3 oligodendroglioma. At the time of the first diagnosis, 15 patients (28.8%) underwent an R0 resection, 29 patients (55.8%) had an R1 resection, and confirmatory biopsy was performed in 8 patients (15.4%). The molecular profile at the time of the primary diagnosis was missing in most patients, as the new WHO classification that considered molecular profiles was updated in 2016 [3], and most patients were included before that date. All patients received radiotherapy, with a dose range of 54–60 Gy (54 Gy for low-grade gliomas and 60 Gy for high-grade gliomas).

All patients included in the analysis experienced a relapse, with a median time to tumor relapse of 19.8 months (range: 5–180 months). Among the patients, 22 (42.3%) underwent salvage surgery, with 12 patients having an R1 resection and 10 patients achieving R0 resection. The median time from the first radiation course to reirradiation was 22.45 months (range: 6.2–166 months), with a median of 21.73 months (range: 15.20–166.57 months) for low-grade gliomas and 21.8 months (range: 6.73–148.33 months) for high-grade tumors.

Based on the reirradiation dose, 24 patients (46%) received 40 Gy in 10 fractions, while 28 patients (54%) received 30 Gy in 5 fractions. The median reirradiation volume (PTV reirradiation) was 64.1 cc (range: 2.6–354 cc).

Nominal total dose and Biologically Effective Dose (BED) from the first and second radiation courses were calculated and evaluated in relation to overall survival. However, no significant differences were found when analyzing the median nominal dose (< 90 Gy *vs.* ≥ 90 Gy) and median BED (<1 90 Gy *vs.* ≥ 190 Gy).

Systemic treatment during reirradiation was administered to some patients, with 16 patients receiving temozolamide, 14 patients receiving bevacizumab, 2 patients receiving irinotecan and bevacizumab, 1 patient receiving lomustine and bevacizumab, and 1 patient receiving pcv (procarbazine, lomustine, and vincristine). Eighteen patients did not receive any systemic agent during reirradiation.

During follow-up, 34 out of 52 patients (65.4%) experienced in-field tumor progression, with a median time to local progression of 5.17 months (range: 3.8–6.4 months) (Fig. 1). Additionally, 13 out of 52 patients (25%) developed out-field relapse, with a median time to distant progression of 4.57 months (range: 2.8-6.2 months). Seven patients (13.5%) had both local and distant failure. Progression was not observed in 12 out of 52 patients (22.2%), with 7 patients not showing progression on MRI, 3 patients not being reevaluated due to death before the first MRI, and 2 patients being lost to follow-up. The median overall survival time from reirradiation to death was 12.03 months (range: 6.05–18 months). At the time of the last follow-up, all but one patient had died.

When stratifying the outcomes based on patient classification, 13 individuals initially diagnosticated with low-grade glioma and 39 individuals with high-grade glioma, the following results were observed. Among high-grade glioma patients, the median survival following reirradiation was 12.5 months (range: 3.2–21.7). For those patients who had previously been diagnosed with low-grade glioma, the median survival post-reirradiation was 10.4 months (range: 3.1–17.7) (Fig. 2).

Univariate analysis (Log Rank test) was performed for local progression-free survival (LPFS), distant progression-free survival (DPFS), and overall survival (OS) as detailed in Table 3. Although no significant relations were found between the analyzed factors and time survival intervals, a trend toward significance was observed with the reirradiation dose and DPFS, favoring patients treated with 30 Gy in 5 fractions ($p = 0.056$). When using the Chi-Square test to analyze differences between groups, a reirradiation dose of 40 Gy in 10 fractions was associated with larger tumors (≥ 64 cc *vs.* < 64 cc; $p = 0.011$) and primary high-grade

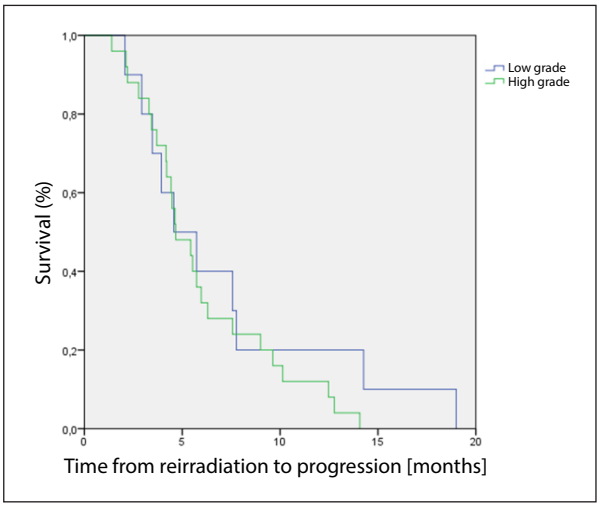


**Figure 1.** Progression free survival

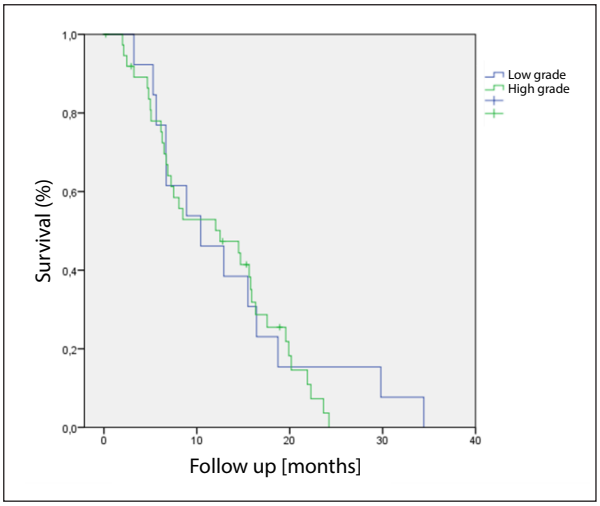


**Figure 2.** Overall survival according to tumor grade

tumors (high *vs*. low; p = 0.00015). A trend toward statistical significance was observed in the fractionation of 40 Gy into 10 fractions among patients who underwent surgery after recurrence compared to those who did not (surgery yes *vs*. no: p = 0.09).

## Tolerance

Treatment was completed without interruptions in all patients within the specified time frame. Tolerance was assessed based on the RTOG/EORTC Common toxicity criteria [11]. The majority of patients tolerated the treatment well, with only three patients (5.7%) experiencing acute Grade-3 toxicity, characterized by repetitive seizures requiring hospitalization. No other acute toxicity of Grade-2 or higher was observed. Radiation necrosis (RN) was diagnosed in six patients (11.2%), but only two patients developed related symptoms.

On univariate analysis, symptomatic radionecrosis was not found to be related to the dose (< or ≥ BED 190; p = 0.22) or reirradiation volume (< or > 64 cc; p = 0.9). In general, neurological dete-

**Table 3.** Tumor and treatment characteristics at reirradiation

| Tumor and treatment characteristics at reirradiation | |
|---|---|
| **Reirradiation median volume [cc]** | 64 (range: 2.6–354) |
| **Surgery** | |
| Yes | 25 (48.1%) |
| No | 27 (51.9%) |
| **Reintervention histology** | |
| GII | 1 (1.9%) |
| GIII | 4 (7.7%) |
| GIV | 20 (38,5) |
| **Surgical resection** | |
| Complete resection | 10 (19.2%) |
| Non complete resection | 15(28.8%) |
| **IDH1** | |
| Mutated | 4 (7.7%) |
| Wild type | 1 (1.9%) |
| Non-applicable | 20 (38.5%) |
| **IDH2** | |
| Mutated | 1 (1.9%) |
| Wild type | 2 (3.8%) |
| Non-applicable | 22 (42.3%) |
| **MGMT** | |
| Metilated | 3 (5.8%) |
| Non-metilated | 1 (1.9%) |
| Non-applicable | 21 (40.5%) |
| **1p19q** | |
| Co-deletion | 2 (3.8%) |
| Non-applicable | 23 (44.2%) |
| **RT dose** | |
| 30 Gy in 5 fractions | 28 (54%) |
| 40 Gy in 10 fractions | 24 (46%) |
| **Systemic therapies** | |
| TMZ | 16 (30.7%) |
| BVZ | 14 (27%) |
| NO | 18 (34.6%) |
| Others | 4 (7.7%) |

RT — radiotherapy; G — grade; TMZ — temozolamide; BEV — bevacizumab; NO — none

rioration was directly correlated with disease progression during follow-up.

## Discussion

Recurrent high-grade glioma poses a significant therapeutic challenge due to the absence of an established standard treatment protocol. However, emerging evidence in the literature suggests that certain patients may benefit from local treatment approaches [12, 13]. Reirradiation of the relapsed area, regardless of prior surgery or systemic therapy, could be a viable therapeutic option for patients with recurrent high-grade glioma. Re-irradiation requires careful patient selection to maximize its potential benefit, precise definition of retreatment volumes, and implementation of advanced radiation treatment protocols. One commonly used strategy in this context is HFSRT, which can be implemented with or without systemic therapy.

HFSRT involves delivering radiation doses in a reduced number of treatment sessions. It encompasses both moderately hypofractionated schedules, typically delivering 2.5–3.5 Gy per fraction, as well as high-dose hypofractionated schedules, where each fraction delivers 5 Gy or more. Numerous studies in the existing literature have extensively investigated the use of HFSRT with a linear accelerator as a reirradiation approach for managing recurrent high-grade gliomas. Importantly, these studies emphasize the minimal occurrence of adverse effects associated with this treatment modality.

The optimal dose for reirradiation remains an area that has not been definitively determined. Striking the delicate balance between maximizing the benefits in terms of local control and progression-free survival while mitigating the potential risks of toxicity associated with repeated irradiation has resulted in the utilization of various treatment schedules (Tab. 4). The usage of HFSRT for recurrent glioma reirradiation exhibits substantial heterogeneity within and across studies. Variations in radiation doses, prescription objectives, fractionation schedules, and staggering techniques contribute to the variability among these regimens. As there are no phase III trials specifically designed to directly compare the efficacy and safety of the various treatment regimens used in reirradiation, the available evidence is largely derived from retrospective studies. Consequently, comparing the radiobiological effects of these different approaches becomes challenging. In our study, we employed two HFSRT regimens judged to be equivalent: 30 Gy delivered in 5 fractions of 6 Gy and 40 Gy delivered in 10 fractions of 4 Gy. The selection of the specific scheme was based on the treating physician's discretion.

Similarly, there is a lack of evidence regarding the optimal chemotherapy regimen to be used in reirradiation. Various published studies have explored the association of different agents such as temozolomide and bevacizumab, or even the exclusion of chemotherapy altogether. In our study, we did not find differences in OS or radionecrosis concerning the use of bevacizumab (yes *vs*. no; $p = 0.667$), even regardless of the timing of treatment (bevacizumab pre-reirradiation, concomitant reirradiation, at least 2 months after reirradiation; $p = 0.405$). However, a recent meta-analysis [13] and a study from Canada [14] have shown that concurrent bevacizumab is an independent protective factor against radiation necrosis and may improve OS.

In our series, 65.4% of the patients experienced in-field tumor progression during the follow-up, with a median time to local progression of 5.17 months (range: 3.8–6.4 months) and a median time to distant progression of 4.57 months (range: 2.8-6.2 months). Regarding OS, the literature reports a range of 6 months [15] to 17.7 months [16]. Similarly, PFS varies from 3 months [17] to 12 months [18]. In our study, the median overall survival time from reirradiation was 12.03 months (range: 6.05–18 months). At the time of the last follow-up, all but one patient had died. These figures align with previously published data and fall within the higher range. It is noteworthy that Raynaud et al. reported an OS of 15 months.

Regarding tumor volume, our study included a larger irradiation volume than reported in the literature, with a median of 64 mL and a range of 2.6–354 cc. Despite having larger tumor recurrences, we did not observe a direct impact on OS or PFS when compared to other series. However, a study from Sunnybrook [14] demonstrated that a re-RT PTV volume < 112 cc [hazard ratio (HR): 0.27, $p < 0.001$] was prognostic for improved OS.

We observed a trend towards improved progression-free survival among patients treated with the shorter 5-fraction scheme. However, this find-

**Table 4.** Univariant analysis results for local progression-free survival (LPFS), distant progression-free survival (DPFS), and overall survival (OS)

| | LPFS | | | | DPFS | | | | OS | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Median survival time (95% CI) | 6 months (%) | 12 months (%) | P (Log Rank test) | Median survival time (95% CI) | 6 months (%) | 12 months (%) | P (Log Rank test) | Median survival time (95% CI) | 6 months (%) | 12 months (%) | P (Log Rank test) |
| Total | 5.17 (3.8–6.4) | 36.4 | 12.1 | | 4.57(2.8–6.2) | 20 | 0 | | 12,03(6.05–18) | 75.6% | 49% | |
| **Age** | | | | | | | | | | | | |
| < 55 | 4.43 (3.8–5) | 23.1 | 7.7 | 0.95 | 4.43 (3.1–5.7) | 14.3 | 0 | 0.77 | 7.5 (5.4–9.5) | 66.7% | 38.1% | 0.270 |
| ≥ 55 | 4.63 (3.4–5.8) | 31.3 | 0 | | 5.53 (3.9–7) | 0 | 0 | | 12.03 (7.26–16.7) | 75.3% | 46% | |
| **Sex** | | | | | | | | | | | | |
| Male | 5.43 (3.9–6.9) | 31.8 | 13.6 | 0.24 | 3.93 (0.3–7.5) | 0 | 0 | 0.44 | 12.03 (4.5–19.5) | 72.5% | 48.3% | 0.932 |
| Female | 4.43 (3.2–5.6) | 27.3 | 0 | | 4.57 (3.2–5.9) | 16.7 | 0 | | 10.43 (0.7–20.1) | 75% | 45% | |
| **Grade** | | | | | | | | | | | | |
| High | 4.67 (3.2–6.2) | 33.3 | 12.5 | 0.77 | 5.53 (3.2–7.9) | 20 | 0 | 0.32 | 12.5 (3.2–21.7) | 75.2% | 50.1% | 0.57 |
| Low | 5.1)7 (3.4–6.9 | 33.3 | 0 | | 4.57 (3.2–5.9) | 0 | 0 | | 10.4(3.1–17.7) | 69.2% | 38.5% | |
| **Surgery at relapse** | | | | | | | | | | | | |
| Yes | 7.23 (3.9–10.5) | 50 | 10 | 0.23 | 3.43 (0–7) | 0 | 0 | 0.64 | 12.5(2.2–22.8) | 71.4% | 47.6% | 0.42 |
| No | 4.63 (4.3–4.9) | 26.1 | 8.7 | | 4.57 (3.2–5.9) | 16.7 | 0 | | 12 (4.8–19.1) | 75.2% | 46.6% | |
| **PTV Volume** | | | | | | | | | | | | |
| < 64 cc | 4.57 (3.1–5.9) | 26.3 | 5.3 | 0.35 | 5.53 (1.2–9.8) | 25 | 0 | 0.09 | 14.5 (4.2–24.7) | 79.5% | 54.4% | 0.306 |
| ≥ 64 cc | 5.43 (2.4–8.4) | 42.9 | 14.3 | | 3.93 (2.7–5.2= | 0 | 0 | | 8.5(3.7–13.2) | 68% | 40% | |
| **Time to reirradiation** | | | | | | | | | | | | |
| < 22 months | 4.47 (4–4.9) | 25 | 0 | 0.23 | 5.53 (3.7–7.3) | 25 | 0 | 0.11 | 8.5 (6.2–10.7) | 68.4% | 40.2% | 0.150 |
| ≥ 22 months | 5.97 (3.7–8.2) | 41.2 | 17.6 | | 2.07 (2–4.5) | 0 | 0 | | 14.7 (8.7–20.6) | 79.2% | 54.2% | |
| **Reirradiation dose** | | | | | | | | | | | | |
| 40 Gy/10 fx | 4.7 (3.3–6) | 28.6 | 7.1 | 0.85 | 3.93 (2.7–5.1) | 0 | 0 | 0.056 | 8.07 (5.3–10.8) | 66.7% | 33.3% | 0.282 |
| 30 Gy/5 fx | 5.4 (3.8–7) | 10.5 | 36.8 | | 5.73 (1.4–10) | 25 | 0 | | 14.5 (10.2–18.7) | 78.8% | 57.3% | |

CI — confidence interval; PTV — planning target volume

**Table 5.** Summary table of selected publications reporting hypofractionated stereotactic radiosurgery in recurrent gliomas

| Ref. | Study type | N°. patients | Histology | Re-irradiation | | EQD2 | Median interval between RT-reRT (months) | Median tumor volume (ml) | Median PFS (months) | Median OS | Severe toxicity (%) | Radionecrosis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Total dose (median) | Dose /fraction (median) | | | | | | | |
| Ernst-Stecken et al. [23], 2007 | P | 15 | 10 GBM, 3 G3 gliomas. 2 G2 gliomas | 35 | 7 | 78.7 Gy | 10 | 22.4 | 15 | 12 | 20% need to increase steroids dose with NEPD | NR |
| Fokas et al. [18], 2009 | P | 53 | All GBM | 30 | 3 | 37.5 Gy | NR | 35 | 22% at 12m | 9 | 0 | 0 |
| Fogh et al. [24], 2010 | R | 147 | 105 GBM, 42 G3 gliomas | 35 | 3.5 | 48.1 Gy | 8 | 22 | NR | 11 | 0.7 | 0 |
| Mckenzie et al. [25], 2013 | P | 33 | 29 GBM, 4 G3glioma | 30 | 5 | 52.5 Gy | NR | 8.5 | 62% at 6m | 8.6 | 9% toxicity other than necrosis | 9 |
| Ogura et al. [17], 2013 | R | 30 | 15 GBM, 9 G3 gliomas. 6 G2 gliomas | 35 | 7 | 78.7 Gy | NR | 9 | 3 | 10.2 | 13.3% need to increase steroids with NEPD | 6.1 |
| Miwa et al. [26], 2014 | P | 21 | All GBM | 30 | 5 | 52.5 Gy | 12 | 27.4 | NR | 11 | 4.8 | 9.5 |
| Dincoglan et al. [27], 2015 | R | 28 | All GBM | 25 | 5 | 43.8 Gy | 11.2 | 36.5 | 5.8 | 10.3 | 0 | 11 |
| Reynaud et al. [28] 2018 | | 32 | GBM | 30Gy | 5 | 52.5Gy | 22.8 | 6.1mL | 3.7 | 15.6m | NR | 12.5% GI |
| Kaul et al. [29] 2020 | R | 133 | GBM | 41.8-49.4/ | 3.5 | 60.6 | 14 | 61.9mL | NR | 6 | NR | 7.6% |
| Ciammella et al. [30] 2022 | P | 12 | GBM | 37.3Gy | 6-10 Gy | 78.8 | 11 m | 47,7mL | 5.7 | 10.4 | 12% | 12% |
| Ehret et al. [19] 2023 | R | 88 | GBM Wild Type | NR | NR | 42.8 Gy | 16.5 | 98mL | 5.9 | 8 | NR | NR |
| Moore-Palhares [14] 2023 | R | 79 | GBM and G3 gliomas | 17–24 Gy/1 Fx (9%), 20–35 Gy/5 Fx (38%), 25–35 Gy/10 Fx (48%) 36-54 Gy/18-30Fx (5%) | | 40 | NR | 112 | 4.1 | 9.9 | NR | 11.3 |
| López et al. 2023 | R | 52 | G2 and G3 gliomas, GBM | 35 | 5–10 | 55 Gy | 22.45 | 64 | 5.17 | 12.043 | 5.7 | 11.2 |

P — prospective; R — retrospective; EQD2 — equivalent dose in 2Gy fractions; GBM — glioblastoma multiforme, G — grade; Nº — number; ReRT — reirradiation; NR — non reported; PFS — progression free survival; OS — overall survival; NEPD — no evidence of progression disease; NA — not available

ing may be attributed to bias in dose prescription and selection of the irradiation schedule based on repeat surgery. Without a strict protocol based on PTV volume, physicians tended to prescribe 30 Gy in 5 fractions for smaller relapses (< 3 cm) and 40 Gy in 10 fractions for larger relapses.

In contrast to literature [19] where previous surgery for tumor relapse has a favorable impact on survival, our study found that patients who underwent prior interventions did not have better outcomes in terms of survival compared to those who did not undergo surgery before reirradiation. Additionally, patients who had previous interventions often received a treatment regimen of 10 fractions of 4 Gy, as the surgical site often encompassed a larger volume.

Survival after re-irradiation has been associated with various prognostic factors. Improving clinical outcomes in recurrent glioblastoma multiforme heavily relies on appropriate patient selection. International guidelines recommend considering reirradiation for young patients with good performance status, particularly if a significant amount of time has passed since their prior radiation treatment. Combs et al [20] showed in their first analysis that the strongest prognostic factors that significantly impacted on survival after re-irradiation were histology, age at diagnosis and the time between initial radiotherapy and re-irradiation ≤ 12 *vs*. > 12 months. In the updated data of their prognostic score-report from the Radiation Oncology Group (ROG) of the German Cancer Consortium (DKTK) [21], they found that all factors including time from primary RT to re-RT, the reresection status, primary histology, age, Karnofsky Performance Scale (KPS), and tumor volume were significantly related to survival. A study published in 2023 finding a median OS of 8 months post-treatment and key factors affecting OS included age, WHO grade, and tumor size [22].

In our series, the median overall survival time from reirradiation was 12.03 months (range: 6.05–18 months), and the median time to local progression was 5.17 months (range: 3.8–6.4 months), which aligns with data reported in the literature. Nevertheless, in comparison to other series, our study included a larger irradiated volume, with a median of 64 mL and a wide range of 2.6–354 cc. Despite the presence of larger tumor recurrences in our cohort, we did not observe a significant impact on OS or PFS when compared to the findings reported in other series. The absence of statistically significant results observed in our series may be attributed to the rigorous patient selection criteria utilized in determining eligibility for reirradiation However, when we analyzed those factors, we did not find any significant relation and could not consider them as predictive factors. One possible explanation for the lack of statistically significant results in our series could be the strict patient selection criteria employed when determining reirradiation eligibility. These criteria may have included factors such as a minimum time interval of 6 months between the initial treatment and reirradiation, an ECOG score of 0–2, and a relatively homogenous and a limited sample size. These stringent criteria potentially contributed to a narrower patient population, limiting the statistical power to detect significant differences in the study outcomes. We acknowledge several limitations and weaknesses in our analysis. Firstly, the retrospective nature of the study introduces inherent biases and may compromise the reliability of the results. Conducting a prospective study would have yielded more robust and unbiased data. Additionally, the small sample size of patients included in our analysis limits the generalizability and wide acceptance of our findings. The limited number of participants reduces the statistical power and hinders drawing definitive conclusions. A larger and more diverse sample would be necessary to strengthen the validity of our results.

Furthermore, we recognize that the decision to offer reirradiation can be contentious due to the complex and inconclusive evidence available in these cases. On the other hand, our experience demonstrates that reirradiation for relapsed high-grade gliomas, in carefully selected patients, is both safe (with low rates of acute toxicity and radionecrosis) and effective. It can achieve a median PFS of 5.17 months and OS of 12.03 months. This is particularly notable in a scenario where all available potential treatments have limited evidence and require further exploration.

Therefore, the decision to reirradiate should be personalized, taking into account a comprehensive assessment of the patient's specific characteristics, tumor features, and the risks and benefits associated with radiotherapy. Informed treatment decisions should involve multidisciplinary discussions

among radiation and medical oncologists and surgeons. This collaborative approach ensures that all relevant perspectives are considered and facilitates the development of the most appropriate treatment strategy for each patient.

Further research and well-designed studies are necessary to gain a better understanding of the role of reirradiation in managing relapsed brain tumors and its impact on long-term outcomes. These future studies should aim to address the limitations of previous research and provide more robust evidence to effectively guide clinical practice.

## Conclusion

HSRT utilizing either 40 Gy in 10 fractions or 30 Gy in 5 fractions is a viable and well-tolerated approach for relapsed high-grade gliomas, demonstrating promising survival rates. However, additional randomized trials are needed to assess the true efficacy of radiotherapy in treating relapsed high-grade gliomas.

### Conflict of interest

Authors declare no conflict of interests.

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