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Stereotactic Radiotherapy in Recurrent Glioblastoma: A Valid Salvage Treatment Option

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Keywords
Glioblastoma · Stereotactic radiotherapy · Salvage treatment · CyberKnife · Re-irradiation

Abstract
Background: Glioblastoma (GBM) is a dismal disease. Recurrence is inevitable despite initial surgery and postoperative temozolomide (TMZ) and radiotherapy. Salvage surgery is the standard treatment in selected patients. Chemotherapy, biological agents, and re-irradiation are other treatment approaches available. Stereotactic radiotherapy (SRT) is nowadays a common treatment as a salvage treatment option. ***Materials and Methods:*** We reviewed the files of 132 GBM cases treated between 2010 and 2018. All patients received TMZ and radiotherapy after surgery or biopsy. Among the patients who had recurrence, we identified 42 cases treated with salvage SRT. The CyberKnife robotic system was used to administer SRT. ***Results:*** While the median follow-up time for all patients was 16 months (range 1–123), the median follow-up time for patients treated with SRT after initial diagnosis was 26.5 months (range 9–123). The median follow-up time after SRT was 10 months (range 2–107). SRT was performed in a median of 3 fractions (range 2–5). The median prescription dose was 20 Gy (range 18–30). While the median actuarial survival after initial diagnosis for patients treated with salvage SRT was 30 months (range 9–123), it was only 14 months (range 1–111) for patients who could not be treated with salvage SRT ($p = 0.001$). The median survival time after SRT was 12 months, and 1- and 2-year survival rates were 48 and 9%, respectively. The time to progression after SRT was 5 months (range 1–62), and 6-month and 1-year progression-free survival rates were 50 and 22%, respectively. Patients with longer time to recurrence >12 months had longer overall survival with respect to the ones having recurrence <12 months ($p < 0.001$). Salvage surgery had been performed in 7 out of 42 patients before SRT. These reoperated patients had significantly worse survival after SRT when compared to the patients who underwent SRT alone ($p = 0.02$). SRT was well tolerated and there was no grade III/IV toxicity. ***Conclusions:*** SRT is a viable salvage treatment option for recurrent GBM. SRT provides acceptable local control and survival benefit for recurrent GBM cases. SRT can be considered especially in patients with long time to recurrence.

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Introduction

Glioblastoma (GBM) is the most common primary brain tumor in adults [1]. Maximal surgical resection followed by adjuvant chemoradiotherapy has been accepted as the standard of care for newly diagnosed cases after the landmark European Organisation for Research and Treatment of Cancer (EORTC) trial [2]. However, the prognosis despite this multimodal treatment remains poor, with a median survival of 14.6 months [2]. Recurrences are inevitable in the majority of cases despite this aggressive adjuvant treatment [2, 3]. Most of the recurrences are observed within the initial tumor bed or irradiated volume [4, 5]. The median overall survival (OS) for patients with recurrent GBM reported in the literature ranges between 5.3 and 24 months [6–12]. There is no standard salvage treatment after recurrence. Most of the patients are considered for symptomatic supportive care. In cases with good performance status, re-resection, re-irradiation, systemic therapy, or combinations thereof can be considered as salvage treatment [13].

Re-resection with complete tumor removal is the preferred treatment in selected patients and may provide a survival advantage [14]. Bevacizumab with or without chemotherapy is an option in cases with good performance status and with no re-resection possibility [15]. Re-irradiation is another treatment modality when re-resection cannot be performed. However, secondary irradiation with conventional fractionation and radiation techniques is highly toxic in already irradiated patients. Stereotactic radiotherapy (SRT) may be an alternative salvage treatment for recurrent GBM. SRT delivers high radiation doses in single or several fractions and provides a radiobiological advantage for radioresistant and recurrent tumors. SRT delivers highly focused radiotherapy to the tumor and spares surrounding critical structures successfully. Several retrospective series demonstrated the efficacy of SRT [4, 16, 17]. However, there is still insufficient evidence about the use of SRT in patients with recurrent GBM.

Nowadays SRT is a preferred treatment option when re-irradiation is planned for recurrent GBM [18–20]. In this study, we aimed to present the clinical outcomes of patients treated with SRT as a salvage treatment option for recurrent GBM.

Materials and Methods

We reviewed the files of 132 GBM cases treated in our clinic between 2010 and 2018. All of these patients received temozolomide (TMZ) and radiotherapy after surgery or biopsy. Among the patients who had recurrence, we identified 42 who were treated with SRT. The patients who received SRT were selected with respect to tumor size, performance status, and interval between initial radiation and recurrence. SRT was planned when the recurrence was observed at least 6 months after previous radiotherapy, when the patient's Karnofsky performance status (KPS) score was >60, and when the recurrent tumor size was <6 cm. SRT was performed with the CyberKnife system (Accuray Inc., Sunnyvale, CA, USA).

We evaluated the OS and progression-free survival (PFS) of patients treated with salvage SRT. The patients – either with progression or recurrence after initial irradiation and who were not treated with SRT for salvage – were compared with patients treated with salvage SRT.

Radiotherapy Technique and Treatment Planning

The CyberKnife system consists of a 6-MV linear accelerator mounted to a robotic arm, coupled with a digital X-ray imaging system. Patients were immobilized using a noninvasive device: a "3-point" thermoplastic mask prepared at the time of planning computed tomography (CT). CT and magnetic resonance imaging (MRI) studies with a slice thickness of 1 mm were obtained in the treatment position. MRI and CT image fusion, contouring, and dose planning were performed using the dedicated inverse planning software Multiplan (Accuray®). The treatment plan of a representative patient is shown in Figure 1.

Gross tumor volume was defined as the contrast-enhanced area on T1-weighted images in MRI. While the clinical target volume was equal to gross tumor volume, a 2-mm margin was added to construct the planning target volume. Real-time images were obtained through X-ray cameras and skull-based tracking was used, i.e., repositioning by reference to the bony structures of the skull. All patients completed the planned treatment without any interruption.

Follow-Up

Patients were followed radiologically with MRI with contrast, which was performed every 1–3 months or as clinically indicated. Magnetic resonance spectroscopy and magnetic resonance perfusion were performed for cases when discrimination of tumor progression or radionecrosis was not possible. Local control was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [21].

Statistics

OS represents the time from initial diagnosis to death or the last control date, PFS after SRT represents the time from SRT to progression, and OS after SRT represents the time from SRT to death or the last control date. OS, PFS, and OS after SRT were evaluated with the Kaplan-Meier method. Prognostic factors for OS, PFS, and OS after SRT as well as comparison of patients who received or did not receive salvage SRT after recurrence were evaluated using log-rank test and Cox regression analysis. We considered a p value <0.05 as significant. All statistical analyses were performed using the SPSS 17.0 software.

Results

Patient and Treatment Characteristics

We analyzed 132 patients after primary radiotherapy. Patients who had recurrence in their follow-up were in-

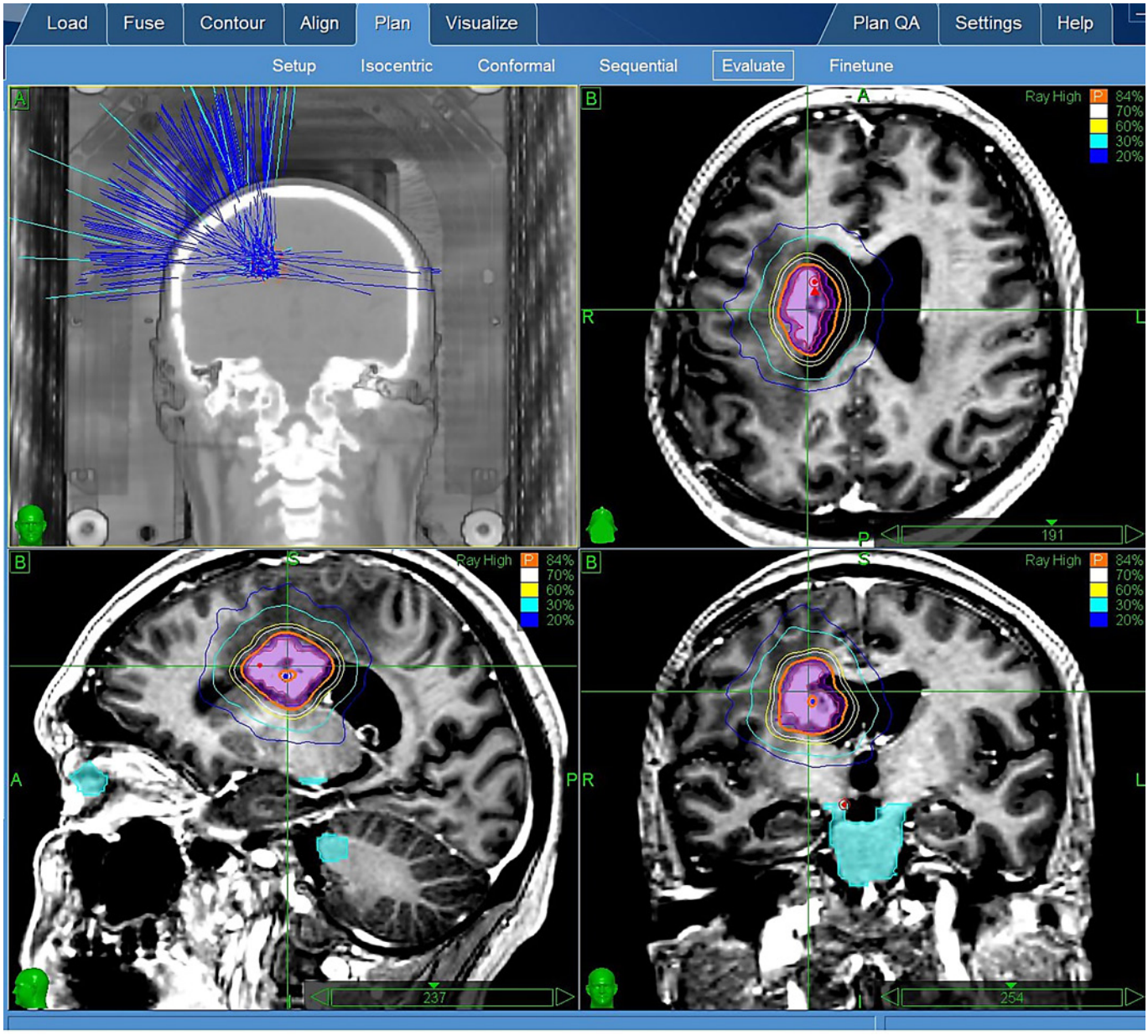

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Fig. 1. Treatment plan of a representative patient.

cluded in the study. We identified 42 patients who were treated with SRT. Among these patients 23 were male, 19 were female, and the median age was 53 years. The initial operation in these patients was gross total resection in 26 patients, subtotal resection in 12 patients, and biopsy only in 4 patients. Initial radiotherapy in 42 patients was planned either by conformal or intensity-modulated technique. All patients were treated with 2-Gy fraction doses per day, 5 fractions per week to a total dose of 60 Gy in 6 weeks. Forty patients (95.2%) received TMZ 75 mg/m^2 daily throughout the radiotherapy followed by adjuvant 6 cycles of TMZ 150–200 mg/m^2 (days 1–5) every 4 weeks after irradiation.

Recurrences were identified within the previous radiation field (infield) in 32 cases, outside the previous radiation field (out-of-field) in 7 cases, and at the margin of the previous radiation field (marginal) in 3 cases. Reoperation was performed in 7 cases before they were referred to our clinic; in 6 cases, it was subtotal resection and in 1 case it was gross total resection.

Table 1. Patient characteristics and treatment parameters

	Incidence	Median (range)
Sex		
Male	23 (55%)	
Female	19 (45%)	
Age, years		53 (19–77)
Initial surgical resection type		
Gross total resection	26 (62%)	
Subtotal resection	12 (27%)	
Biopsy	4 (11%)	
Adjuvant radiotherapy technique		
Conformal	30 (71%)	
IMRT	12 (29%)	
Median radiotherapy dose, Gy	60 (100%)	
Median fractions	30 (100%)	
Adjuvant TMZ treatment		
Yes	40 (95%)	
No	2 (5%)	
Adjuvant TMZ cycle		6 (2–12)
Location of recurrence		
Infield	32 (76%)	
Marginal	3 (7%)	
Out-of-field	7 (17%)	
Salvage surgery before SRT		
Yes	7 (17%)	
No	35 (83%)	
Surgical resection type at recurrence		
Gross total resection	1 (2%)	
Subtotal resection	6 (14%)	
KPS score before SRT		80 (70–100)
KPS score after SRT		80 (60–90)
Recurrence tumor volume (GTV), cm^3		10.8 (1–101.3)
Recurrence tumor diameter, mm		26 (5–60)
SRT dose, Gy		20 (18–30)
SRT fractions		3 (2–5)
Biologically equivalent dose, Gy		40 (28.8–52.8)
Median conformity index		1.23 (1.08–2.52)
New conformity index		1.29 (1.12–7.54)
Homogeneity index		1.19 (1.09–1.43)
Prescription isodose line, %		84 (70–92)
Salvage chemotherapy after SRT		
Yes	33 (79%)	
No	9 (21%)	

GTV, gross tumor volume; IMRT, intensity-modulated radiotherapy; KPS, Karnofsky performance status; SRT, stereotactic radiotherapy; TMZ, temozolomide.

SRT was performed in a median of 3 fractions (range 2–5) and the median prescription dose was 20 Gy (range 18–30), which was biologically equivalent to a dose of 40 Gy (range 28.8–52.8). The SRT parameters were as follows: the median conformity index, the new conformity index, and the homogeneity index were calculated as 1.23 (range 1.08–2.52), 1.29 (range 1.12–7.54), and 1.19 (range 1.09–1.43), respectively. The median tumor diameter and volume were 26 mm (range 5–60) and 10.8 cm^3 (range 1–101.3), respectively. Following SRT, 33 of 42 (78.5%) patients received salvage systemic therapy, including TMZ (17 patients), bevacizumab and irinotecan combination (14 patients), and irinotecan only (2 patients). The patient characteristics and treatment parameters of the salvage SRT group are summarized in Table 1.

Clinical Outcomes

While the median follow-up time after initial diagnosis for all patients was 16 months (range 1–123), it was 26.5 months (range 9–123) in patients who were treated with salvage SRT. The median time between initial radiotherapy and SRT was 13 months (range 5–40). The median follow-up time after SRT was 10 months (range 2–107). At the time of analysis, only 7 of the 42 patients (16.6%) were alive.

After SRT, all patients had at least one radiologic evaluation, with a median of 2 MRI scans (range 1–12) per patient. According to RECIST, complete response was observed in 3 patients (7%), partial response in 11 patients (26%), stable disease in 12 patients (29%), and progressive disease in 16 patients (38%) during the first 3 months after SRT. Four patients died with disease progression in the first 3 months.

While the median actuarial survival after initial diagnosis for patients who were treated with salvage SRT was 30 months (range 9–123), it was only 14 months (range 1–111) for patients who could not be treated with salvage SRT ($p = 0.001$). The median survival time after SRT was 12 months, and 1- and 2-year survival rates were 48 and 9%, respectively. The time to progression after SRT was 5 months (range 1–62), and 6-month and 1-year PFS rates were 50 and 22%, respectively. The median survival of patients who were treated with salvage SRT from the date of initial diagnosis as well as the PFS and median survival from the date of salvage SRT are represented in Figure 2a–c.

Although it was not statistically significant, the greater the extent of initial surgical resection, the longer the OS as well as the PFS and the OS after SRT were, and the p values were 0.16, 0.13, and 0.1, respectively. Patients

with longer time to recurrence >12 months had longer OS with respect to the ones having recurrence <12 months ($p < 0.001$), but PFS and OS after SRT were not improved significantly depending on time of recurrence (p values were 0.63 and 0.09, respectively). Recurrence location was not significantly associated with OS or PFS and OS after SRT. Salvage surgery had been performed in 7 out of 42 patients before SRT. These reoperated patients had significantly worse survival after SRT when compared to the patients who underwent SRT alone ($p = 0.02$).

No correlation was found between treatment characteristics (median conformity index, new conformity index, homogeneity index, gross tumor volume, biologically equivalent dose value, number of fractions, prescription isodose, use of salvage chemotherapy) and patient characteristics (age, sex, and KPS score at salvage treatment) on OS as well as PFS and OS after SRT. Table 2 summarizes the univariate analysis results of patients who were treated with salvage SRT.

Toxicity

SRT was well tolerated and there were no grade III/IV toxicities such as radionecrosis or focal neurologic deficits during the follow-up period. Grade I/II toxicities such as nausea, headache, or vomiting may have occurred, but were not noted.

Discussion

Despite surgery and adjuvant chemoradiotherapy, the prognosis remains poor and recurrences are observed in the majority of patients. There is no standard salvage treatment in recurrent GBM. Salvage treatment options include surgery, chemotherapy, and re-irradiation. SRT has the benefit of being a noninvasive procedure which delivers a high dose of radiation to the target volume while minimizing toxicity in adjacent normal tissues, and it can be an alternative to salvage surgery. Although there are retrospective series demonstrating the efficacy of SRT performed for recurrent small-volume GBM, SRT is not a standard treatment in recurrent cases [4, 16, 17].

Previous studies demonstrated a survival benefit of SRT when compared with observation for recurrent GBM patients [16]. Hau et al. [22] indicated that patients who were treated with SRT after recurrence had a longer median survival than patients who were observed (8.2 months vs. 2.2 months). Kondziolka et al. [23] reported a median survival of 30 months from the time of initial diagnosis in 64 patients with recurrent GBM treated with

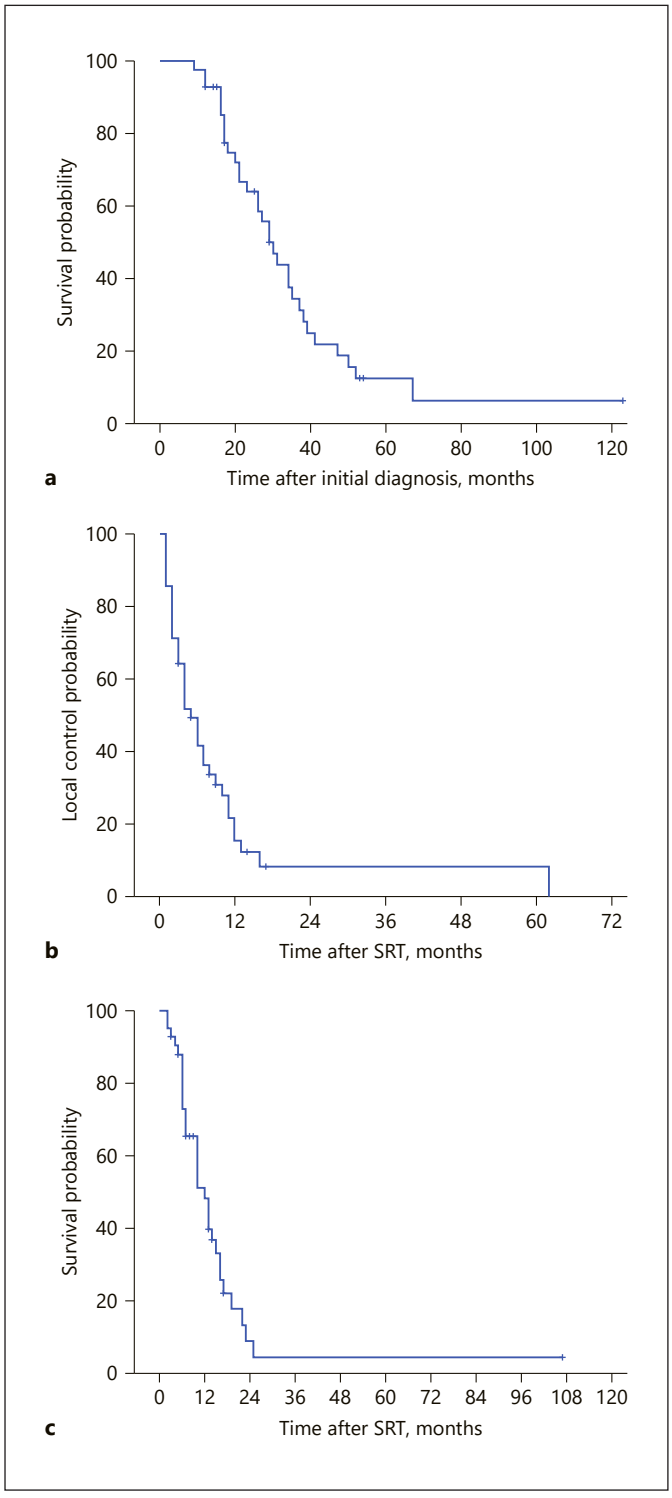

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Fig. 2. a Survival curve of the patients from the initial diagnosis. **b** PFS curve of the patients after SRT. **c** Survival curve of the patients after SRT. PFS, progression-free survival; SRT, stereotactic radiotherapy.

Table 2. Univariate analysis of variables with influence on survival

	OS	*p*	OS after SRT	*p*	PFS after SRT	*p*
Age		0.61		0.84		0.74
≤52 years	31 months		13 months		6 months	
>52 years	19 months		10 months		4 months	
Gross tumor volume		0.54		0.96		0.6
≤11 cm^3	31 months		13 months		5 months	
>11 cm^3	29 months		12 months		6 months	
Biologically equivalent dose		0.22		0.44		0.88
≤40 Gy	21 months		10 months		6 months	
>40 Gy	34 months		12 months		4 months	
Initial surgical resection type		0.16		0.1		0.13
Gross total resection	34 months		14 months		7 months	
Subtotal resection	21 months		10 months		2 months	
Biopsy	20 months		6 months		3 months	
Salvage surgery before SRT		0.46		0.02		0.1
Yes	29 months		6 months		4 months	
No	30 months		13 months		6 months	
Time to recurrence		<0.001		0.09		0.63
≤12 months	18 months		10 months		4 months	
>12 months	37 months		14 months		6 months	
Salvage chemotherapy after SRT		0.78		0.5		0.97
Yes	29 months		13 months		5 months	
No	31 months		10 months		6 months	

OS, overall survival; PFS, progression-free survival; SRT, stereotactic radiotherapy.

SRT, while Gutin et al. [24] found a median PFS and OS of 7.3 and 12.5 months, respectively, after salvage SRT for recurrent GBM. Vordermark et al. [25] found a median PFS and OS of 4.6 and 7.9 months, respectively, after re-irradiation with SRT. Our survival results are comparable with the results in the literature. We found a median OS of 30 months, and PFS and OS after SRT were 5 and 12 months, respectively.

A long time interval between initial diagnosis and recurrence was found as a prognostic factor for survival in previous studies [26–28]. Hasan et al. [29] demonstrated that salvage SRT provided longer OS in patients when the time to recurrence was >16 months with respect to the patients with shorter time to recurrence <16 months. We found that when the time interval between initial diagnosis and recurrence was >12 months, OS was longer with respect to the patients having recurrence <12 months ($p < 0.001$). On the other hand, PFS and OS after salvage SRT were not significantly different depending on early or late recurrence.

Besides time of recurrence, several studies investigating the role of salvage SRT in recurrent GBM demonstrated that tumor volume was another important prognostic factor for survival [7, 26, 30, 31]. Patients with large recurrent tumors (>42 mm) were reported to have shorter OS in the pooled analysis of the EORTC Brain Tumor Group clinical trials [32]. We did not find any correlation between tumor volume and survival after salvage SRT. Radiation dose is another parameter that may have an effect on the results of salvage SRT. In a retrospective study including 19 patients which investigated the effect of radiation dose on survival [25], patients treated with an SRT dose >30 Gy had significantly superior OS compared to patients who received <30 Gy (11.1 vs. 7.4 months, $p = 0.05$). In a recent meta-analysis no dose-response relationship was demonstrated for doses >36 Gy or <36 Gy (2-Gy equivalent doses) [33]. In our study there was no correlation with SRT dose and survival.

Addition of systemic therapies to SRT was investigated as well. Conti et al. [34] evaluated the effect of

"dose-dense" administration of TMZ together with salvage SRT in recurrent GBM patients. In this trial, median survival and median time to progression were significantly better when salvage SRT was combined with TMZ with respect to SRT alone (12 vs. 7 months, $p < 0.01$; 7 vs. 4 months, $p = 0.01$). In a study evaluating the impact of adding bevacizumab to SRT for recurrent GBM patients, both OS (median 8.6 vs. 5.7 months) and PFS (median 5.6 vs. 2.5 months) were significantly increased when bevacizumab was added [35]. A recent meta-analysis did not demonstrate any significant difference between the studies which employed concurrent systemic therapy and those which employed no concurrent systemic therapy [33]. In our study, 33 of the patients received chemotherapy sequentially but not concomitantly after salvage SRT. We found no impact of the use of post-SRT chemotherapy on PFS and OS. Addition of emerging molecularly targeted agents, especially against angiogenesis inhibition with or without TMZ, were investigated in several phase I–II trials, with promising results in newly diagnosed GBM patients [36]. These agents may be considered in salvage treatment as well as together with SRT.

Salvage surgery is the standard treatment option for selected patients who are young with good performance status and have a long interval between initial treatment and recurrence. In different reoperation series the reported median survival ranged from 3 to 9 months [37–41]. Although initial surgery at the time of diagnoses provides a survival advantage in GBM treatment, re-resection before re-irradiation had no significant impact on survival [41]. In a study including 147 recurrent GBM patients, 84 had salvage surgery prior to re-irradiation, with no beneficial effect of resection on OS ($p = 0.513$) [14]. Park et al. [42] in their retrospective study investigated preoperative risk factors for recurrent GBM patients. They found that tumor location near critical structures, poor KPS score, and high tumor volume (≥50 mL) indicate poor survival after reoperation. Another study by Holt et al. [17] found poor survival after subtotal resection of recurrent GBM. In our study, reoperated patients (6 subtotal resection, 1 total resection) before salvage SRT had significantly inferior OS after SRT compared to unoperated ones ($p = 0.02$). Postsurgical morbidity and mortality are important concerns for re-resected patients after recurrence. Skeie et al. [10] reported morbidity and mortality rates of 26.7 and 2.2%, respectively, for reoperated recurrent GBM patients, and the KPS score decreased in the majority of patients. Thus, poor survival of recurrent GBM patients necessitates preoperative risk assessment and good selection of patients if re-resection is planned.

In re-irradiation series radiation necrosis is observed with high frequency, but this complication is not so common when re-irradiation is performed with SRT. In a study which investigated the role of salvage SRT in 84 patients, the authors did not observe any radiation necrosis [43]. In our study, salvage treatment with SRT was well tolerated, and no grade III/IV treatment-related toxicity was noted throughout the follow-up period.

We observed better survival in patients who received SRT for salvage treatment with respect to patients who did not receive it. This survival advantage may result from the effect of SRT as well as the fact that patients treated with SRT consist of selected patients with better prognostic factors. We need to better define the role of SRT in this patient population with prospective studies.

Although being retrospective and having a small patient population size, this study suggests that SRT is a viable salvage treatment option for recurrent GBM with minimal toxicity. SRT provides acceptable local control and survival benefit for recurrent GBM cases.

Conclusion

Recurrence is often observed with dismal prognosis in GBM. There are limited treatment options for these patients. While re-resection with complete removal is the standard treatment approach, SRT may be offered in selected patients with good performance status and long time interval to recurrence. Besides surgery, SRT is nowadays the commonly preferred treatment modality in the radiation oncology community due to better efficacy and lower toxicity with respect to classical re-irradiation methods. Further investigations are warranted for better definition of target volume, optimal timing of treatment, SRT dose and fractionation, and combination with chemotherapeutic/radiosensitizing agents and newer targeted therapies.

Statement of Ethics

Informed consent was obtained from all the patients and the study was approved by the hospital's local ethics committee.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they all participated in the design, execution, and analysis of the study and that they approved the final version of the paper.

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