

Fractionated stereotactic reirradiation and concurrent temozolomide in patients with recurrent glioblastoma

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Abstract The aim of this paper is to evaluate the efficacy of fractionated stereotactic radiotherapy (FSRT) and concomitant temozolomide (TMZ) as a salvage treatment option in patients with recurrent glioblastoma (GBM). Between May 2006 and December 2009, 36 patients with recurrent GBM received FSRT plus concomitant TMZ at University of Rome La Sapienza, Sant' Andrea Hospital. All patients had Karnofsky performance score ≥ 60 and were previously treated with standard conformal radiotherapy (RT) (60 Gy) with concomitant and adjuvant TMZ for 6–12 cycles. The median time interval between primary RT and reirradiation was 14 months. At the time of recurrence, all patients received FSRT plus concomitant daily TMZ at the dose of 75 mg/m², given 7 days per week from the first day of RT. Radiation dose was 37.5 Gy delivered in 15 fractions over 3 weeks. Median overall survival after FSRT was 9.7 months, and the 6- and 12-month survival rates were 84 and 33%, respectively. The

median progression-free survival (PFS) was 5 months, and 6- and 12-month PFS rates were 42 and 8%, respectively. In univariate analysis, KPS ($P = 0.04$), the interval between primary RT and reirradiation ($P = 0.02$), and O6-methylguanine-DNA-methyltransferase (MGMT) methylation status at the time of diagnosis ($P = 0.009$) had an effect on survival; however, in multivariate analysis, only MGMT methylation was statistically significant ($P = 0.03$). In general, FSRT was well tolerated and the treatment was completed in all patients. Neurological deterioration due to radiation-induced necrosis occurred in three patients (8%). FSRT plus concomitant TMZ is a feasible treatment option associated with survival benefits and low risk of complications in selected patients with recurrent GBM. The potential advantages of combined chemoradiation schedules in patients with recurrent GBM need to be explored in future studies.

Keywords Glioblastoma · Fractionated stereotactic radiotherapy · Temozolomide · Recurrence · Reirradiation

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Introduction

Tumor control and survival in patients with glioblastoma (GBM) have improved with the use of radiotherapy (RT) plus concomitant and adjuvant temozolomide (TMZ). In the recent EORTC/NCIC randomized trial, the reported median and 2-year survivals were 14.6 months and 27%; however, the majority of tumors recurred locally within a few months [1].

Chemotherapy, surgery and RT have been employed as salvage treatment for recurrent GBM, with chemotherapy being probably the most frequent treatment option. Although promising survival benefits have been recently

reported with the use of alternative schedules of TMZ and the antiangiogenic agent bevacizumab [2–6], most cytotoxic and targeted agents used as single agents or in combination have shown only modest results in patients with recurrent GBM [7–10]. A surgical approach can be employed in selected patients, but optimal resection is very difficult because of the infiltrative nature of disease, and may be associated with a high risk of morbidity [11, 12]. Stereotactic radiation techniques have emerged as a feasible treatment for recurrent brain tumors that have been previously exposed to high doses of RT [13]. Compared with conventional RT, stereotactic techniques, given as single fraction radiosurgery (SRS) or as fractionated stereotactic RT (FSRT), can deliver more localized irradiation with a steeper dose gradient between tumor and the surrounding normal tissue reducing the risk of radiation-induced complications. In patients with recurrent or progressive GBM, median survivals of 6–10 months have been reported after either SRS [14–20] or FSRT [21–28]. FSRT given in small fractions of 2–3 Gy enables the precision and accuracy of SRS, while maintaining the radiobiological advantages of fractionation in terms of tumor control and protection of surrounding normal brain tissue, and has been employed since 2005 in our department as salvage therapy for recurrent gliomas.

In the current study, we have evaluated the efficacy and toxicity profile of a combined approach of FSRT performed as reirradiation with concomitant TMZ in patients with recurrent GBM.

Patients and methods

Between May 2006 and December 2009, 36 patients with recurrent GBM received FSRT plus concomitant TMZ at the Department of Radiation Oncology of Sant' Andrea Hospital at University of Rome La Sapienza. Patient characteristics are shown in Table 1. There were 22 males and 14 females. The median patient age was 56 years (range 34–72). The *O6*-methylguanine-DNA-methyltransferase (MGMT) promoter evaluated at the time of surgery was methylated in 20 patients and unmethylated in 16 patients, respectively. After DNA extraction, MGMT promoter was determined by chemical modification of unmethylated, but not the methylated, cytosines to uracil and subsequent polymerase-chain-reaction as previously described [29]. All patients had Karnofsky performance score ≥ 60 and were previously treated with standard conformal RT (60 Gy) with concomitant and adjuvant TMZ for 6–12 cycles. All patients were treated for the presence of a recurrent or progressive tumor as showed at MRI occurring at least 3 months after the end of primary treatment. The study was approved by the local Ethical Committee. All patients

Table 1 Characteristics of 36 patients with recurrent glioblastoma

Characteristics	
Age (years)	
Median	56
Range	34–72
Sex	
Male	22
Female	14
Karnofsky performance status	
Median	70
Range	60–100
Site of tumor	
Temporal	11
Frontal	12
Parietal	7
Occipital	6
Extension of resection	
Total	17
Partial/subtotal	19
MGMT methylation status	
Methylated	20
Unmethylated	16
Number of cycles with temozolomide	
6 cycles	29
12 cycles	7
Interval between primary radiation and reirradiation	
Median (months)	14
Range (months)	9–39
Recurrence volume (cm ³)	
Median	13.1
Range 2	1–35.3
Planning target volume (cm ³)	
Median	32.1
Range	12.3–72.4

MGMT O6-methylguanine-DNA-methyltransferase

provided a written informed consent form prior to study participation.

At the time of recurrence, all patients received FSRT plus concomitant daily TMZ at the dose of 75 mg/m² given 7 days per week from the first day of RT. The frameless BrainLab stereotactic system was used for stereotactic reirradiation [30]. CT scanning was done using a slices in thickness and spacing of 1.2 mm acquired throughout the entire cranium. The gross tumor volume (GTV) was delineated on the basis of the contrast-enhancing tumor demonstrated on T1-weighted MRI fused with the simulation CT images, using an automatic fusion algorithm. The planning target volume (PTV) was generated by the geometric expansion of GTV plus 3–5 mm. Critical structures contoured were brainstem, optic nerves, chiasm, and eyes.

Treatment volumes were achieved with multiple noncoplanar beams shaped using a micromultileaf collimator (MLC). All patients were treated on a 6-MV LINAC with a 120 leaf MLC (Varian Clinac 600 DBX). Treatment dose was 37.5 Gy prescribed to the 90% isodose line and delivered in 15 fractions over 3 weeks. A verification CT scan was obtained immediately before the treatment to evaluate the relocation accuracy of the isocenter that had to be less than 1.5 mm. Anteroposterior and right lateral portal film images (Varian Medical Systems, Palo Alto, CA, USA) were obtained daily during the treatment. The median PTV was 32.1 cm³ (12.3–72.4 cm³).

After treatment, all patients were followed with serial neurologic and radiologic examinations. Follow-up MRI were obtained routinely every 2 months after the end of FSRT, or in the event of neurological deterioration. Complete response was defined as complete resolution of tumor by neuroimaging studies. Partial response was defined as a decrease in tumor size (2 diameters) by 50% or greater. Minor response was defined as a decrease in tumor size of <50%, and stable disease was defined as <25% change in tumor size. Progressive disease was defined as >25% increase in tumor size or development of a new lesion on imaging studies. Toxicity was evaluated using the National Cancer Institute's Common Toxicity Criteria, version 3.0. Radionecrosis was defined clinically as neurologic deterioration, associated with increased contrast enhancement within the treatment volume that improved with the use of steroids and was maintained for at least 2 months. Perfusion MRI and fluorodeoxyglucose positron emission tomography were used in order to distinguish radionecrosis from recurrent tumor.

The primary endpoint of this analysis was overall survival (OS). Secondary endpoints included progression-free survival (PFS) and tolerance to treatment. OS and PFS were estimated using the Kaplan–Meier method calculated from the time of reirradiation. OS and PFS were stratified by age, MGMT promoter methylation status at the time of surgery, KPS, site of tumor, interval between primary treatment and recurrence, extension of resection, and tumor volume. Univariate analysis and multivariate Cox proportional hazards regression model were used to test the effect of prognostic factors on survivals.

Results

Between May 2006 and December 2009, 36 patients with recurrent GBM received FSRT plus concomitant TMZ. The median interval between primary RT and reirradiation was 14 months. Twenty-nine patients received 6 cycles of TMZ and 7 patients 12 cycles of TMZ as part of their primary treatment. No patients were lost during the follow-

up. Eight patients were alive at the time point of analysis; 28 patients died of tumor progression during follow-up.

OS and PFS

The median OS after FSRT was 9.7 months (Fig. 1). Six- and 12-month survival rates were 84 and 33%, respectively. The median PFS was 5 months, and 6- and 12-month PFS rates were 42 and 8%, respectively (Fig. 2). At progression after FSRT, further treatments included surgery in three patients, TMZ in five patients and bevacizumab in three patients.

In univariate analysis, KPS ($KPS \leq 70$ vs $KPS > 70$, $P = 0.04$; log-rank test), interval between primary RT and reirradiation ($P = 0.02$) and MGMT methylation status at the time of diagnosis ($P = 0.009$) were statistically significant (Table 2). The median survival was 11.3 months in methylated patients and 7.9 months in unmethylated patients (Fig. 3). Six- and 12-month OS rates were 90 and 38% in methylated patients and 80 and 12% in unmethylated patients ($P = 0.02$ at 12 months), respectively. Sex, age, tumor volume, tumor site and extension of resection had no effect on survival. In multivariate Cox proportional hazards regression model, MGMT methylation status was the only independent prognostic factor (RR 0.40; 95% CI 0.19–0.94; $P = 0.03$). Methylated MGMT had also an independent effect on PFS (RR 0.38; 95% CI 0.18–0.79; $P = 0.01$). The median PFS was 7 months in methylated patients and 3 months in unmethylated patients (Fig. 4). Age, sex, KPS, tumor site, extension of resection and tumor volume were not significant prognostic factors.

Median OS from primary treatment was 23.4 months (Fig. 5). In univariate analysis, KPS ($KPS \leq 70$ vs $KPS > 70$, $P = 0.02$), extension of resection (total vs subtotal/

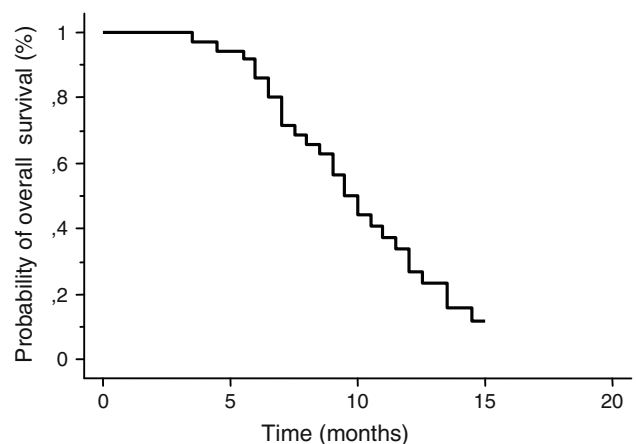


Fig. 1 Kaplan–Meier analysis of overall survival in 36 patients after reirradiation for recurrent glioblastoma treated with fractionated stereotactic radiotherapy (FSRT) and temozolomide

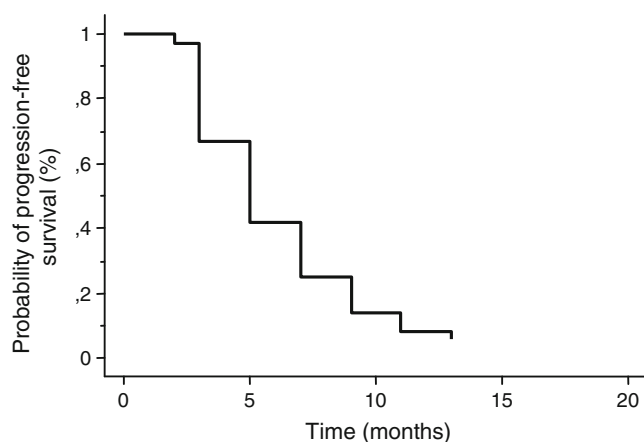


Fig. 2 Kaplan–Meier analysis of progression-free survival after reirradiation in 36 patients with recurrent glioblastoma treated with fractionated stereotactic radiotherapy and temozolomide

partial removal; $P = 0.008$) and MGMT methylation status ($P = 0.001$) were statistically significant. The median OS was 26.8 months in methylated patients and 19.7 months in unmethylated patients, respectively. There was a trend of increasing survival in patients <50 years old ($P = 0.1$). In multivariate Cox proportional hazards regression model complete resection (RR 0.46; 95% CI 0.2–0.96; $P = 0.04$) and MGMT methylation status (RR 0.35; 95% CI 0.15–0.76; $P = 0.02$) were independent favorable prognostic factors.

A partial response was observed in four methylated patients (Fig. 6) and a minimal response in seven patients (five methylated and two unmethylated patients). Twenty patients required dexamethasone at the time of FSRT; during the subsequent follow-up, six patients discontinued and eight patients reduced dexamethasone.

Table 2 Prognostic factors in 36 patients with recurrent GBM treated with FSRT plus TMZ

	OS			PFS		
	Median (months)	Univariate analysis P	Multivariate analysis P	Median (months)	Univariate analysis P	Multivariate analysis P
All patients	9.7	NS	–	5	NS	–
Age						
Sex		NS			NS	
Male	9.5		–	5		–
Female	10.1		–	5		–
Site of tumor		NS			NS	
Temporal	9.7		–	5		–
Frontal	11		–	7		–
Parietal	8.9		–	5		–
Occipital	9.2		–	5		–
KPS score		0.04	NS		NS	
60–70	8.7			5		–
80–100	10.1			5		–
Extension of resection		NS			NS	
Total	10.1		–	5		–
Partial/subtotal	9.3		–	5		–
Previous cycles of TMZ		NS			NS	
6 cycles	9.3		–	5		–
12 cycles	10.4		–	7		–
MGMT methylation status		0.009	0.03*		0.005	0.01**
Methylated	11.3			3		
Unmethylated	7.9			7		
Recurrence volume	–	NS	–	–	NS	–
Interval from initial diagnosis	14	0.02	NS	–	0.1	–

NS not significant, OS overall survival, PFS progression-free survival, MGMT O6-methylguanine-DNA-methyltransferase, FSRT fractionated stereotactic radiotherapy, TMZ temozolomide

* RR 0.40; 95% CI 0.19–0.94

** RR 0.38; 95% CI 0.18–0.79

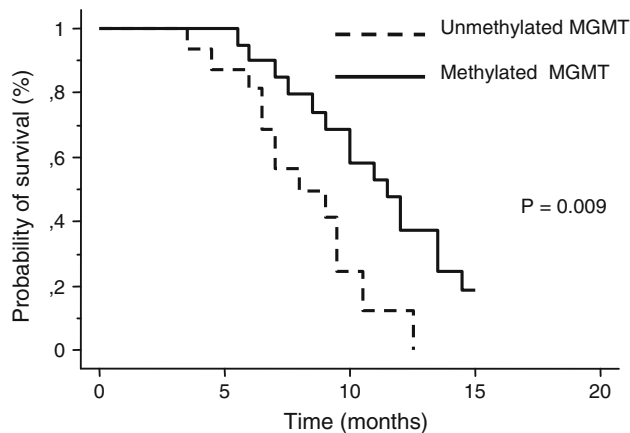


Fig. 3 Kaplan–Meier analysis of overall survival after reirradiation in 36 patients with recurrent glioblastoma treated with fractionated stereotactic radiotherapy and temozolomide according to MGMT promoter methylation status. There was a significant longer survival in methylated patients ($P = 0.009$, log-rank test)

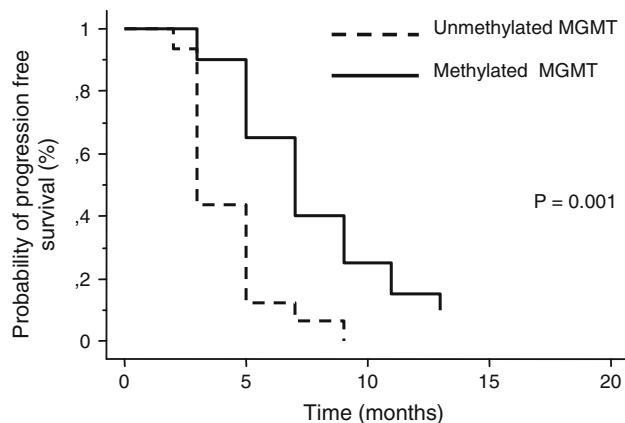


Fig. 4 Kaplan–Meier analysis of progression-free survival after reirradiation in 36 patients with recurrent glioblastoma treated with fractionated stereotactic radiotherapy and temozolomide according to MGMT promoter methylation status. There was a significant longer progression-free survival in methylated patients ($P = 0.001$, log-rank test)

Toxicity

In general, FSRT was well tolerated, and the treatment was completed without interruption in all patients. The most common adverse event was a moderate-to-severe fatigue, which occurred in 15 patients (41%). One patient had grade 3 thrombocytopenia during the last week of FSRT. Neurological deterioration due to radiation-induced necrosis occurred in three patients (8%) at 5, 7 and 9 months after FSRT and was managed successfully with dexamethasone. No other severe late side effects were reported.

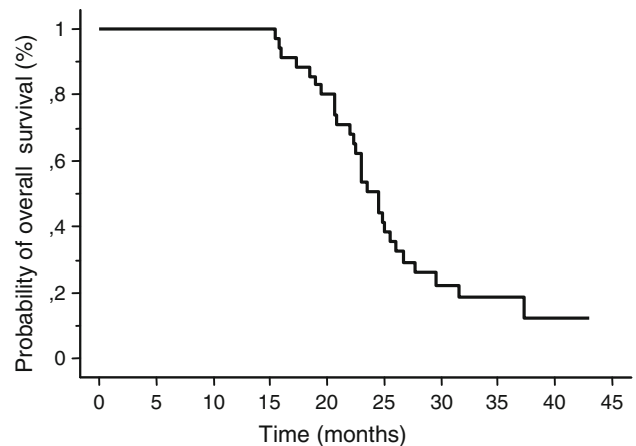


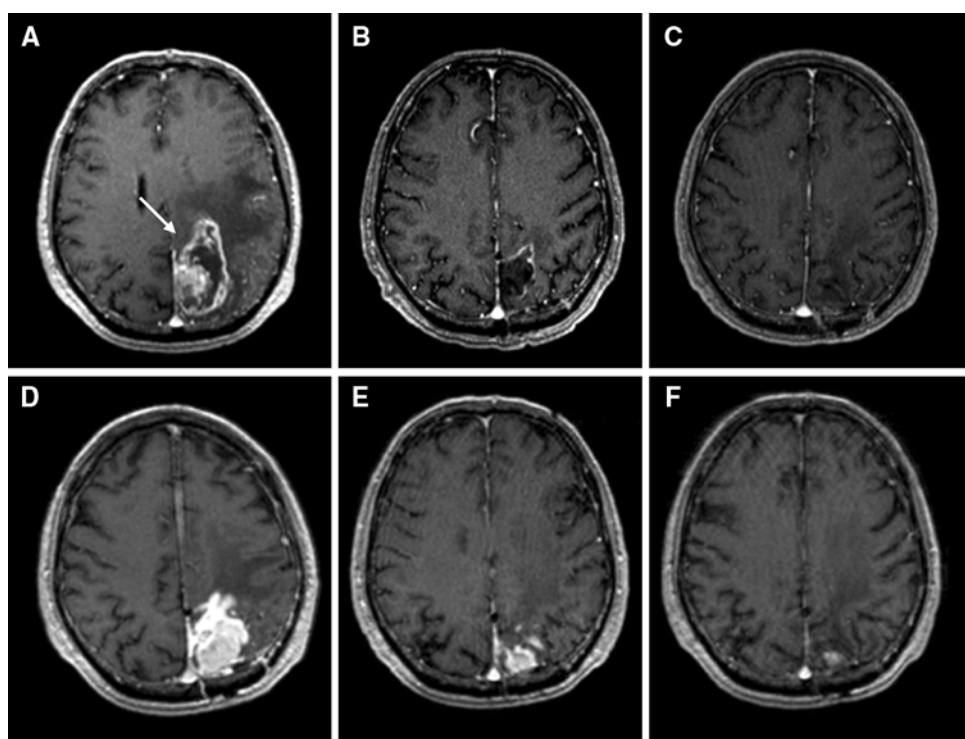
Fig. 5 Kaplan–Meier analysis of overall survival from the time of initial diagnosis in 36 patients reirradiated for recurrent glioblastoma with fractionated stereotactic radiotherapy (FSRT) and temozolomide

Discussion

FSRT has been reported as an effective treatment option in patients with recurrent high-grade gliomas [20–28]. Combs et al. [23] treated 59 patients with GBM with FSRT at a dose of 36 Gy delivered in 2-Gy fractions, reporting a median and 1-year survival rates of 8 months and 23%, with respective PFS rates of 5 months and 5%. Cho et al. [20] using FSRT at a dose of 37.5 Gy in a median fractionation of 5×2.5 Gy/week, as for our study, observed a median survival of 7.1 months in 42 patients with recurrent GBM, and similar survivals of 7–11 months have been shown by others with FSRT delivered in fractions of 3.5–6 Gy to a total dose of 30–40 Gy [23–28].

The current study reports the results in a series of patients with recurrent GBM who received FSRT plus concomitant TMZ. Median OS and PFS were 9.7 and 5 months, respectively. Six- and 12-month OS rates were 84 and 33%, respectively, and the respective PFS rates were 42 and 8%. The use of TMZ in addition to RT was based on the observation that concurrent chemotherapy can potentiate the cytotoxicity of radiation. Preclinical and in vitro data have in fact shown that the contribution of TMZ to irradiation is at least additive and can even be synergistic [31–33], and the cytotoxic effect of concomitant TMZ to RT has been suggested in patients with newly diagnosed GBM [34]. The combination of fractionated RT and concurrent chemotherapy in recurrent high-grade gliomas has been explored in few studies [35–39]. In a series of 25 patients with recurrent gliomas treated at the Department of Radiation Oncology at the University of Heidelberg with FSRT at a dose of 36 Gy in 2-Gy fractions in combination with TMZ, the reported median OS and PFS from reirradiation were 8 and 5 months, respectively [38]. Actuarial 6- and 12-month OS rates were 81 and 25%, respectively,

Fig. 6 Axial T1 post-contrast MRI scans of a patient with partial response of a recurrent GBM to fractionated stereotactic radiotherapy (FSRT) and temozolomide. At diagnosis, the patient showed a large parietal enhancing mass with irregular contrast enhancement (*arrow*) (**a**). Histology confirmed the presence of a methylated GBM. Three weeks after surgery (**b**), the patient received standard radiotherapy plus concomitant and adjuvant temozolomide, showing a tumor complete response (**c**). Twenty months after the primary treatment, the tumor recurred (**d**) and was treated with FSRT plus concomitant temozolomide. The MRI scans performed 2 and 6 months after the end of treatment show progressive decrease of the tumor (**e, f**)



and respective PFS rates 48 and 16%. In a series of 44 patients with recurrent high-grade gliomas, Grosu et al. [37] reported a median survival time of 11 months for patients who received FSRT plus TMZ and 6 months for patients treated with FSRT without TMZ ($P = 0.008$). Arcicasa et al. [36] treated 31 patients with malignant gliomas with external beam RT at a total dose of 34.5 Gy in 23 fractions over 4.5 weeks in combination with lomustine, reporting a median PFS and OS of 8.4 and 13.7 months, respectively.

Although published data suggest that combined chemoradiation in patients with recurrent GBM is more effective than radiation alone, it is not possible to prove that survival benefits reported in our study were the result of the addition of TMZ to FSRT rather than a reflection of patient selection. In fact, only patients with more favorable disease who did not progress during the primary chemoradiation received reirradiation plus TMZ, and this is likely to represent a selection bias. Nevertheless, alternative dose schedules of TMZ in recurrent GBM have been associated with survival benefits in patients who experienced progression during conventional adjuvant TMZ therapy or after a TMZ-free interval, as reported in some recent published series [3, 4, 39]. In our Institution, we have started a prospective study to explore the potential survival advantages of FSRT plus concomitant and adjuvant dose-dense TMZ in patients with recurrent high-grade gliomas.

SRS has been employed in patients with recurrent GBM as a treatment alternative. Shrieve et al. [15] have shown median survival times of 10.2 months in 86 patients with

recurrent GBM treated with SRS at a median dose of 13 Gy, with 1- and 2-year survivals of 45 and 19%, respectively. Survival in the range of 7–11 months comparable with FSRT has been reported by others [16–20]; however, with an incidence of severe treatment-related side effects in up to one-third of patients when SRS was used for relatively larger volumes $>30 \text{ cm}^3$ [14, 15, 20].

In recent years, the efficacy of the anti-angiogenic agent bevacizumab has been evaluated in patients with recurrent GBM in several clinical trials [5, 6, 40]. Friedman et al. [5] have reported on 167 patients with recurrent GBM who were randomly assigned to receive bevacizumab alone or in combination with irinotecan. The 6-month PFS and the median OS times were 42.6% and 9.2 months in patients treated with bevacizumab, and 50.3% and 8.7 months in patients treated with bevacizumab and irinotecan, respectively. Kreisl et al. [6] in 48 patients with recurrent GBM treated with bevacizumab as single agent have shown a similar 6-month PFS and OS rates of 29 and 57%, respectively. Thromboembolic events and hypertension reported in 12% of patients were the most common drug-associated adverse events. As a result of the encouraging data obtained in these trials, bevacizumab has been approved in the USA (but not in Europe) as monotherapy in patients with GBM who progressed after initial treatment. Although bevacizumab appears to be an effective agent in recurrent GBM, the majority of patients do not achieve durable disease control. Interestingly, Gutin et al. [41] using hypofractionated SRT in combination with

bevacizumab in 25 patients with recurrent high-grade gliomas reported a promising 6-month PFS of 65% and 1-year survival of 54%. The potential additive effects of RT to alkylating and targeted agents in order to improve the clinical outcome in patients with recurrent GBM need to be explored in future prospective trials.

Analysis of prognostic factors showed that KPS, the interval between primary RT and reirradiation, and MGMT methylation status at the time of diagnosis were significant prognostic factors for survival; however, in multivariate analysis, only MGMT methylation was statistically significant. OS and PFS rates were 11.2 and 7 months in methylated patients and 7.9 and 3 months in unmethylated patients, respectively. MGMT promoter methylation has been shown to be associated with improved outcome in GBM and appears to be a predictive biomarker sensitivity for benefit from either TMZ chemotherapy [42] or RT alone [43]. Although the relative values of radiation and chemotherapy could not be extrapolated from our study, the favorable outcome in methylated patients seems to indicate that, at least in a subset of patients with recurrent GBM, methylated MGMT promoter at diagnosis retains its prognostic value, and combined chemoradiation treatment may represent a valuable therapeutic option. In contrast, the median time interval between reirradiation and tumor progression of unmethylated tumors was only 3 months, suggesting that different radiation schedules and chemotherapeutic agents should be considered in such patients. In our Institution, we have started a prospective study to test the potential efficacy of FSRT plus concomitant and adjuvant dose-intense TMZ in patients with recurrent high-grade gliomas.

The risk of severe radiation-induced complications after reirradiation is of concern in patients previously treated with high-dose standard RT. Acute effects were mild, and only one patient presented grade III haematological toxicity during treatment. Neurological deterioration due to radiation-induced necrosis occurred in 8% of patients and was manageable with steroids. A low incidence of acute and late toxicity in patients with recurrent GBM using FSRT alone or in association with TMZ has been reported previously [20, 22, 23, 37, 38], suggesting that fractionated reirradiation, at least in fractions of 2–3.5 Gy for a total dose less than 40 Gy, may be a better treatment option for patients with larger tumors or tumors in eloquent structures.

In conclusion, FSRT plus concomitant TMZ for patients with recurrent GBM is a feasible treatment associated with low toxicity; however, the survival benefits are modest. Methylated patients with longer stable disease after primary standard chemoradiation have the better outcome, suggesting that methylation status of MGMT promoter also retains its prognostic value in recurrent GBM. The potential

advantages of combined chemoradiation schedules to further improve outcome in patients with recurrent GBM need to be explored in future studies.

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