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Survival and Prognostic Factors in Re-irradiation for Recurrent/ Progressive Malignant Gliomas: Turkish Society of Radiation Oncology Neuro-Oncology Group, TROD 007-006 Study

Birsen YUCEL[1], Dicle ASLAN[2], Gokhan YAPRAK[3], Yıldız GUNEY[4], Petek ERPOLAT[5], Oguz CETINAYAK[6], F. Ilknur KAYALI[7], Celalettin EROGLU[2], Naciye ISIK[3], Eda ERDIS[1]

[1]Sivas Cumhuriyet University Faculty of Medicine, Department of Radiation Oncology, Sivas, Türkiye
[2]Erciyes University Faculty of Medicine, Department of Radiation Oncology, Kayseri, Türkiye
[3]Istanbul Kartal Dr. Lutfi Kirdar Training and Research Hospital Radiation Oncology, Istanbul, Türkiye
[4]Yuksek Ihtisas University, Department of Radiation Oncology Memorial Hospital, Ankara, Türkiye
[5]Gazi University Faculty of Medicine, Department of Radiation Oncology, Ankara, Türkiye
[6]Dokuz Eylul University Faculty of Medicine, Department of Radiation Oncology, Izmir, Türkiye
[7]Ankara Bilkent City Hospital, Department of Radiation Oncology, Ankara, Türkiye

Corresponding author: Birsen YUCEL ✉ yucelbirsen@yahoo.com

ABSTRACT

AIM: To evaluate survival and prognostic factors associated with survival among patients who underwent reirradiation for recurrent/ progressive primary brain tumors.

MATERIAL and METHODS: A multicenter, retrospective study (7 centers, N=236) was conducted by the Neuro-oncology Group of the Turkish Radiation Oncology Association.

RESULTS: Median overall survival (OS) was 11 months and 1- and 2-year survival rates were 48% and 22%, respectively. Survival was negatively correlated with cumulative biologically effective dose (BED10) (r=-0.158, p=0.016) and cumulative equivalent dose in 2-Gy fractions (EQD2) (r=-0.158, p=0.016). In univariate analysis, survival was associated with performance status (p<0.001), histopathology at diagnosis and recurrence (p<0.001), radiotherapy (RT) method used for recurrence (p=0.025), tumor volume at recurrence (p=0.014), cumulative EQD2 (<110 vs. ≥110 Gy, p=0.038), and cumulative BED10 (<130 vs. ≥130 Gy, p=0.022). In multivariate analysis, tumor volume at recurrence (HR=1.68, 95% CI=1.06-2.64, p=0.025), Karnofsky Performance Status score (HR=5.7, 95% CI=3.26-9.98, p<0.001), and histopathology at recurrence (glioblastoma vs. high-grade glioma: HR=0.48, 95% CI=0.26-0.88, p=0.019; glioblastoma vs. low-grade glial tumor: HR=0.16, 95% CI=0.08-0.34, p<0.001) were found to be independent prognostic factors. Radionecrosis was detected in 25% (n=58) of the patients. Re-resection was associated with a higher rate of radionecrosis (37.7% vs. 18%, p=0.002).

CONCLUSION: The prognostic factors most strongly associated with survival in glioma patients undergoing reirradiation were Karnofsky Performance Status score below 70, glioblastoma histopathology, and tumor volume greater than 4.5 cm^3. In addition, survival time was negatively correlated with cumulative EQD2 and BED10. The rate of radionecrosis was higher in patients who underwent re-resection compared those who did not.

KEYWORDS: Malignant glioma, Reirradiation, Survival

Birsen YUCEL : 0000-0002-0083-6866
Dicle ASLAN : 0000-0002-3716-3925
Gokhan YAPRAK : 0000-0001-8521-8073
Yildiz GUNEY : 0000-0003-2251-3571
Petek ERPOLAT : 0000-0001-6793-8157
Oguz CETINAYAK : 0000-0002-8823-8341
F. Ilknur KAYALI : 0000-0002-0649-115X
Celalettin EROGLU : 0000-0002-5743-2440
Naciye ISIK : 0000-0002-7444-5913
Eda ERDIS : 0000-0003-3003-8643

INTRODUCTION

Brain tumor recurrence and progression pose a major problem in terms of treatment. Gliomas are primarily treated surgically, but the limited ability to perform total gross resection at diagnosis and the infiltrative nature of these tumors result in a high risk of recurrence (23). Therefore, radiotherapy (RT) or chemoradiotherapy is often used in the adjuvant treatment of gliomas to reduce the likelihood of recurrence (23). Treatment options for recurrent malignant gliomas include reoperation, systemic chemotherapy, reirradiation, or a combination of these therapies. However, there is still no satisfactory solution to the problem of deciding which patients should receive which treatment. The use of re-resection is often limited because of the infiltrative nature of these tumors, as well as the severe neurological deficits and high mortality rates associated with further surgical interventions (3,16,24). Systemic chemotherapy provides only limited palliation with the regimens available. With reirradiation, the biggest concern is the potential to cause radionecrosis (1,2,7,17,25).

Henke et al. reported that 69% of recurrent brain tumors occurred within the RT field, 10% occurred at the edge of the RT field, and 21% occurred outside the RT field (9). As most recurrences are within the RT field, the brain tissue's tolerance to radiation is extremely important, and knowing the tolerance of brain tissue is key to the applicability of reirradiation (9). Our increased understanding of brain tissue tolerance to radiation and ability to more accurately describe target volumes as a result of advances in RT and imaging technology have increased the use of reirradiation. Since the first report of the reirradiation of recurrent brain tumors in 1996, studies have demonstrated the applicability of this treatment paradigm (1,2,7,9,17,25).

However, a careful benefit-risk assessment is necessary when selecting patients to undergo reirradiation. The best approach is to select individuals who it is believed will benefit most from the treatment. In this regard, a combination of prognostic factors identified in studies may aid in personalizing the potential benefits of reirradiation. Researchers such as Combs et al. and Kessel et al. developed prognostic scoring systems based on prognostic factors such as the patient's age, time from primary RT to reirradiation (RT interval), histopathology, Karnofsky Performance Status (KPS) score, planning target volume (PTV), and whether re-resection was performed (5,6,11). In addition, some studies have shown that factors such as the radiation dose used in reirradiation, dose fractionation scheme, and re-resection status (gross total resection or subtotal resection) may be important in survival (12,13,18,20,21).

The aim of this study was to evaluate survival and the prognostic factors affecting the survival of patients who underwent reirradiation for recurrent/progressive malignant glioma.

MATERIAL and METHODS

Ethical approval for the study was obtained from the Ethics Committee of Sivas Cumhuriyet University (No: 2019-05/22, Date: 22.05.2019). This study was planned as a multicenter, retrospective study including a total of 236 patients with malignant glioma from 7 centers: 56 patients (24%) from Erciyes University Faculty of Medicine, Radiation Oncology Department, 51 (22%) from Istanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital, Radiation Oncology Department, 47 patients (20%) from Ankara Memorial Hospital, Radiation Oncology Department, 30 patients (13%) from Sivas Cumhuriyet University Faculty of Medicine, Radiation Oncology Department, 27 (11%) from Gazi University Faculty of Medicine, Radiation Oncology Department, 15 (6%) from Dokuz Eylül University Faculty of Medicine, Radiation Oncology Department, and 10 patients (4%) from Ankara Bilkent City Hospital, Radiation Oncology Department.

Inclusion Criteria

Patients over 18 years of age who underwent reirradiation for recurrent/progressive malignant glioma (low- or high-grade) between 2010 and 2020 were selected for this study. The patients' performance status was evaluated using the KPS scale. Primary brain tumors were graded using the World Health Organization (WHO) criteria. In this study, RT interval was determined as the time between the first course of RT and the second course of RT (reirradiation).

Overall survival (OS) was calculated as the time from the date that recurrence/progression was detected and reirradiation was performed to the date of last follow-up or death.

Radiotherapy Techniques

For reirradiation, patients were immobilized in supine position with an Aquaplast mask, and planning computed tomography (pCT) scans with 2-3 mm cross-sections were performed. In all centers, gadolinium-enhanced brain magnetic resonance images (MRI) were fused to the pCT images for better detection of gross target volume (GTV) during contouring. The GTV was marked on MRI T1 sequence images as a contrast-enhancing tumor or tumor cavity. Tumor edema was generally not included in this area. The clinical target volume (CTV) was created by adding a 0-15 mm margin around the GTV based on the selected dose fractionation scheme (conventional fractionated radiotherapy [CFRT], hypofractionated stereotactic radiotherapy [HSRT], or stereotactic radiotherapy [SRT]). The PTV (planning target volume) was contoured by adding a 3-5 mm margin to the CTV.

RT techniques varied according to the centers performing the irradiation. The patients were irradiated using three techniques: 3D conformal RT (3DCRT), intensity-adjusted RT (IMRT), and volumetric arc therapy (VMAT). The RT dose also varied by center and the selected fractionation scheme. Three different dose fractionation schemes were used for reirradiation. CFRT was defined as a fractional dose up to 3 Gy, HFRT as doses of 3 to 8 Gy, and SRT as 8 Gy or more. The schemes were applied as 24-60 Gy/12-30 fractions in CFRT, 15-35 Gy/3-10 fractions in HSRT, and 12-40 Gy/1-3 fractions in SRT.

To express the different dosing schemes in equivalent values, RT doses were calculated as the equivalent dose in 2 Gy per fraction ($EQD_2 = D \times [(d + \alpha/\beta)/(2 + \alpha/\beta)]$). In addition, the

biologically effective dose (BED) was calculated using the formula BED = D (1+d/[α/β]). In these formulas, 'D' represents the total dose and 'd' the daily dose, while α/β = 10 for the tumor and α/β = 3 for the central nervous system (19).

Radionecrosis Assessment

Contrast-enhanced brain MRI was performed at 3-month intervals after reirradiation to evaluate reirradiation results and toxicity. Radionecrosis was diagnosed histopathologically in patients who underwent surgical resection and radiologically by brain MRI in patients who did not undergo surgery.

Statistical Analysis

SPSS version 23 (IBM Corp., Armonk, NY, USA) software was used for statistical analyses. Descriptive tests were used to analyze the patients' demographic characteristics, the Kaplan-Meier test was used to determine survival times, and Cox regression analysis was used to identify independent prognostic factors. Correlation analysis was performed to evaluate the relationships between OS and noncategorical variables such as age, RT dose, and time to relapse. Chi-square tests were used to compare categorical variables (radionecrosis, fractionation scheme, and RT technique). Mann-Whitney U tests were used to compare median cumulative EQD_2, cumulative BED_{10}, and tumor volume values according to the presence of radionecrosis. P values of <0.05 was considered statistically significant.

RESULTS

More than half of the patients were male (58%, n=136) and nearly two-thirds had glioblastoma according to histopathology (72%, n=171). The patients' demographic characteristics and treatments are shown in Table I.

The median survival time was 11 months, 1-year survival was 48%, and 2-year survival was 22%. According to correlation analysis, survival time did not correlate with age (r=-0.108, p=0.100) or time to recurrence (r=0.087, p=0.183), but weak negative correlations with cumulative BED_{10} (r=-0.158, p=0.016) and cumulative EQD_2 (r= -0.158, p=0.016) were observed.

Gender, comorbidity, primary or secondary glioblastoma at recurrence, reoperation, use of chemotherapy for recurrence, use of chemoradiotherapy for recurrence, dose fractionation scheme in reirradiation, and the RT interval were not associated with survival in univariate analysis (p>0.05). However, the patients' performance status (KPS score), pathology at diagnosis and recurrence, RT method used for recurrence,

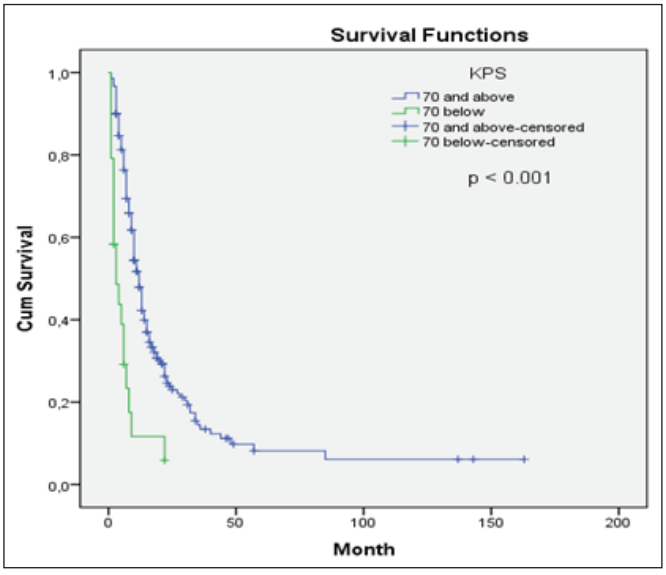

Figure 2: Survival curve by Karnofsky performance status.

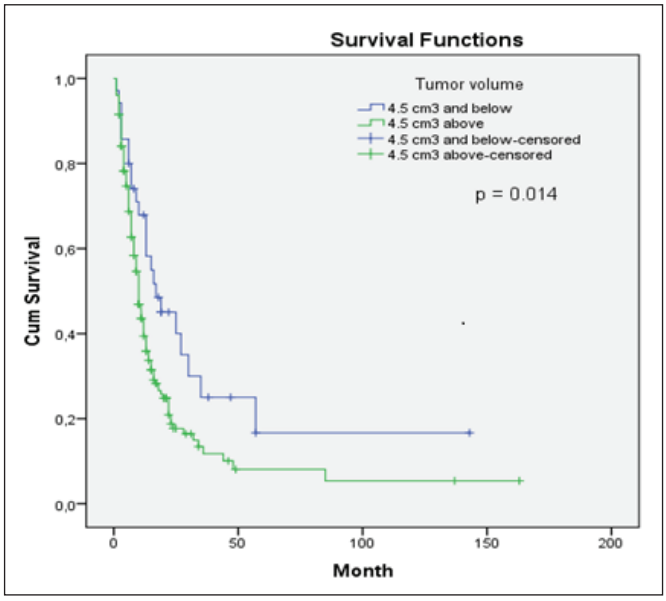

Figure 1: Survival curve by tumor volume.

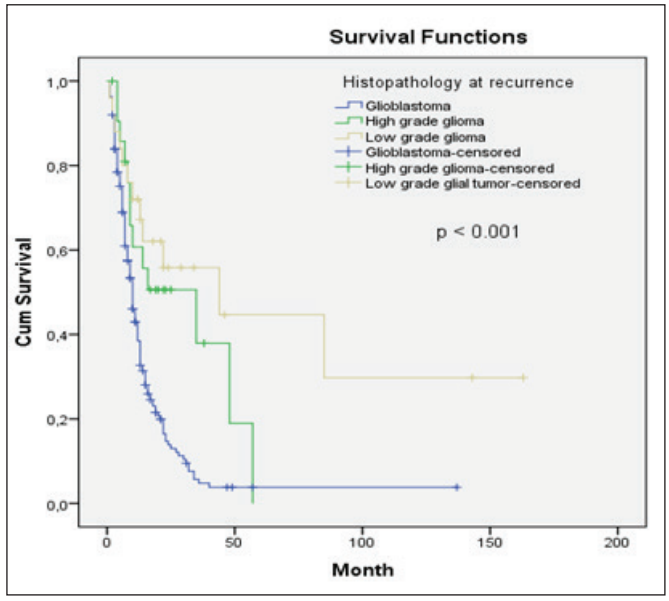

Figure 3: Survival curve by histopathology at recurrence.

PTV at recurrence, cumulative EQD_2, and cumulative BED_{10} were found to be prognostic factors associated with survival ($p<0.050$) (Table II). In multivariate analysis, histopathology at recurrence, performance status, and PTV at recurrence were identified as independent prognostic factors (Table III). Survival curves according to these independent prognostic factors are shown in Figures 1-3.

Radionecrosis was detected in 25% (n=58) of the patients. No significant relationship was found between radionecrosis and dose fractionation scheme (p=0.575). The prevalence of radionecrosis was 25% with CFRT, 20% with HSRT, and 28% with SRT. Re-resection was associated with radionecrosis. The prevalence of radionecrosis was 18% in patients who did not undergo re-resection and 37.7% in those who did (p=0.002). The median cumulative EQD_2, cumulative BED_{10}, and tumor volume were 93.3 (77.35-117.75) Gy, 112 (99-133.81) Gy, and

Table I: Characteristics of Patients and Treatments at Diagnosis and Recurrence

	Patient no. (%)		Patient no. (%)
Sex		KPS at second RT	
Female	100 (42)	KPS ≥70	212 (90)
Male	136 (58)	KPS <70	24 (10)
Initial histopathology		Second histopathology	
Glioblastoma	171 (72)	Glioblastoma	189 (80)
HGG	28 (12)	HGG	22 (9)
LGG	37 (16)	LGG	25 (11)
Initial treatments		Second treatments	
Surgery	220 (93)	Re-resection	87 (37)
Subtotal resection	89 (40)	Chemoradiotherapy	69 (29)
Gross total resection	131 (60)	Chemotherapy	184 (78)
Chemoradiotherapy	194 (82)	Temozolomide	91 (39)
Adjuvant chemotherapy	189 (80)	Bevacizumab	104 (44)
		Irinotecan	106 (45)
Initial RT method		Second RT method	
2DRT	9 (4)	2DRT	0 (0)
3DCRT	63 (27)	3DCRT	7 (3)
IMRT	130 (55)	IMRT	160 (68)
VMAT	34 (14)	VMAT	69 (29)
Initial RT dose fractionation schedule		Second RT dose fractionation schedule	
CFRT	236 (100)	CFRT	90 (38)
		HSRT	92 (40)
		SRT	52 (22)
Median dose in initial RT		Median dose in second RT	
EQD_2 (Gy)	60 (32.5-60)	EQD_2 (Gy)	39.38 (18.75-62)
BED_{10} (Gy)	72 (39-72)	BED_{10} (Gy)	47.25 (22.5-74.4)
Median age at second RT (years)	52 (18-80)	Median cumulative dose	
		EQD_2 (Gy)	97.5 (69.22-117.75)
		BED_{10} (Gy)	117 (83.06-141.3)
RT interval (months)	17 (4-195)	Median tumor volume at second RT (cm^3)	19.15 (0.12-516)
Glioblastoma at recurrence		Median tumor volume (cm^3)	
Primary	171 (90)	CFRT	35.9 (2-356.5)
Secondary	18 (10)	HSRT	14.9 (0.66-516)
		SRT	3.76 (0.12-50)
Increased grade at recurrence	18 (8)	Radionecrosis	58 (25)

KPS: *Karnofsky performance status,* ***HGGT:*** *High-grade glioma,* ***LGG:*** *Low-grade glioma,* ***RT:*** *Radiotherapy,* ***2DRT:*** *Two-dimensional radiotherapy,* ***3DCRT:*** *Three-dimensional conformal radiotherapy,* ***IMRT:*** *Intensity modulated radiotherapy,* ***VMAT:*** *Volumetric modulated arc therapy,* ***CFRT:*** *Conventional fractionated radiotherapy,* ***HSRT:*** *Hypofractionated stereotactic radiotherapy,* ***SRT:*** *Stereotactic radiotherapy,* ***EQD_2:*** *Equivalent dose in 2 Gy fractions,* ***BED:*** *Biologically effective dose.*

Table II: Prognostic Factors Affecting Survival in Reirradiation of Malignant Glioma

Univariate analysis	Patient no. (%)	1-year OS (%)	2-year OS (%)	Median OS (months)	p-value
KPS					
≥70	212 (90)	52	24	12	**<0.001**
<70	24 (10)	6	-	3	
Initial histopathology					
Glioblastoma	171 (72)	41	13	10	
HGG	28 (12)	54	46	14	**<0.001**
LGG	37 (16)	67	45	22	
Second histopathology					
Glioblastoma	189 (80)	43	14	10	
HGG	22 (9)	56	51	35	**<0.001**
LGG	25 (11)	72	56	44	
Glioblastoma at recurrence					
Primary	171 (90)	41	13	10	0.203
Secondary	18 (10)	61	17	12	
Re-resection					
No	149 (63)	45	22	10	0.589
Yes	87 (37)	53	23	12	
CRT at recurrence					
No	167 (71)	47	21	10	0.562
Yes	69 (29)	51	23	12	
CT at recurrence					
No	52 (22)	41	29	10	0.839
Yes	184 (78)	49	20	11	
Second RT method					
3DCRT	7 (3)	29	29	8	
IMRT	160 (68)	44	14	10	**0.025**
VMAT	69 (29)	56	33	13	
Second RT dose fractionation schedule					
CFRT	90 (38)	44	23	10	
HSRT	92 (40)	51	22	12	0.886
SRT	52 (22)	48	18	12	
Tumor volume at second RT					
<4.5 cm^3	36 (15)	68	40	17	**0.014**
≥4.5 cm^3	178 (85)	44	18	10	
Cumulative BED_{10}					
<130 Gy	212 (90)	49	24	11	**0.038**
≥130 Gy	24 (10)	33	9	8	
Cumulative EQD_2					
<110 Gy	212 (90)	49	24	11	**0.022**
≥110 Gy	24 (10)	30	10	8	

KPS: *Karnofsky performance status,* ***OS:*** *Overall survival,* ***HGGT:*** *High-grade glioma,* ***LGG:*** *Low-grade glioma,* ***CRT:*** *Chemoradiotherapy,* ***CT:*** *Chemotherapy,* ***RT:*** *Radiotherapy,* ***3DCRT:*** *Three-dimensional conformal radiotherapy,* ***IMRT:*** *Intensity modulated radiotherapy,* ***VMAT:*** *Volumetric modulated arc therapy,* ***CFRT:*** *Conventional fractionated radiotherapy,* ***HSRT:*** *Hypofractionated stereotactic radiotherapy,* ***SRT:*** *Stereotactic radiotherapy,* ***EQD_2:*** *Equivalent dose in 2 Gy fractions,* ***BED:*** *Biologically effective dose.*

Table III: Independent Prognostic Factors Affecting Survival in Reirradiation of Malignant Glioma

Multivariate analysis	HR	95% CI	p-value
Tumor volume at second RT			
≤4.5 cm^3	1		
>4.5 cm^3	1.68	1.06-2.64	**0.025**
KPS			
KPS ≤70	1		
KPS <70	5.70	3.26-9.98	**<0.001**
Second histopathology			
GBM	1		
HGG	0.48	0.26-0.88	**0.019**
LGG	0.16	0.08-0.34	**<0.001**

***HR:** Hazard ratio, **CI:** Confidence interval, **KPS:** Karnofsky performance status, **GBM:** Glioblastoma, **HGG:** High-grade glioma, **LGG:** Low-grade glioma.*

20.5 (0.22-356.5) cm^3 in patients without radionecrosis and 100 (82.5-111.5) Gy, 120 (99-141.3) Gy, and 14.5 (0.9-516) cm^3 in patients with radionecrosis, respectively. There were no statistically significant differences between the groups (p>0.05).

DISCUSSION

In this study examining survival and the prognostic factors associated with survival in patients with malignant glioma who underwent reirradiation, we determined a median survival time of 11 months and 1- and 2-year OS rates of 48% and 22%, respectively. A KPS score lower than 70, glioblastoma histopathology of the recurrent tumor, and a tumor volume greater than 4.5 cm^3 were found to be independent prognostic factors that adversely affected survival. In addition, survival was negatively correlated with cumulative EQD_2 and cumulative BED_{10}. Radionecrosis was detected in 25% of patients and was more common among those who underwent re-resection compared to those who did not.

There is still no established standard for the treatment of glioma recurrence and progression. As treatment options include re-resection, chemotherapy, reirradiation, and combinations thereof, it seems a rational approach to use prognostic factors to guide treatment decisions. Prognostic factors associated with survival are an important step in the personalization of treatment for these patients. Researchers have contributed to the treatment paradigm by developing prognostic scoring systems. First, Combs et al. developed a scoring system based on prognostic factors identified in 233 patients with glial tumors, 60% of whom had high-grade glioma and underwent reirradiation (fractionated SRT). They showed that histopathology (glioblastoma vs. high-grade glioma vs. low-grade glioma), age (<50 years vs. >50 years), and RT interval (<12 months vs. >12 months) affected survival (5). Later, Kessel et al. and Combs et al. conducted validation studies of the prognostic scoring system and included KPS, PTV, and re-resection to the scoring system in addition to the above prognostic factors (6,11). Table IV summarizes the independent prognostic factors reported in selected studies. In general, the independent prognostic factors most commonly identified in these studies were the patient's age, performance status, RT interval, and grade at recurrence (5,6,8,12-15,18,21). In our study, patient age and RT interval were not significant, while performance status, histopathology at recurrence, and PTV were the most important independent prognostic factors determining survival.

Other reirradiation studies showed that tumor histopathology was the main feature affecting survival. Median OS time and 1-year OS rates in patients with malignant glioma have been reported as 12-21 months and 75% for low-grade glioma, 11-20 months and 57% for high-grade glioma, and 7-9 months and 32% for glioblastoma, respectively (5,6,11,13-15,18,19,21). In a meta-analysis of glioblastoma patients who underwent reirradiation (50 studies, n=2095), Kazmi et al. determined 6-month and 1-year OS rates of 75% and 36%, respectively (10). When the patients in our study were evaluated according to histopathology, both the initial grade and the grade at recurrence were found to affect survival. According to initial pathology, the median, 1-year, and 2-year OS were 22 months, 67%, and 45% in low-grade glioma; 14 months, 54%, and 46% in high-grade glioma; and 10 months, 41%, and 13% in glioblastoma, respectively. According to pathology at recurrence, these values were 44 months, 72%, and 56% in low-grade glioma; 35 months, 56%, and 51% in high-grade glioma; and 10 months, 43%, and 14% in glioblastoma, respectively. In our study, we observed that patients with both low- and high-grade glioma benefited greatly from reirradiation.

The treatment techniques or dose fractionation schemes used in reirradiation may also be among the features affecting survival. For recurrent tumors, dose fractionation schemes such as CFRT, HSRT, or SRT are generally preferred based on tumor diameter. In previous studies, SRT results usually seem better because of the widespread use of SRT for small tumors. Shanker et al. conducted a meta-analysis of survival outcomes according to treatment technique in patients with high-grade glioma (70 studies, n=3302) who underwent reirradiation for recurrence. In multivariate analysis, they found a significant correlation between median OS and RT techniques after adjusting for age, BED of reirradiation, RT interval, and treatment volume. Corrected median OS was 12.2 months with SRT, 10.1 months with HSRT, and 8.9 months with CFRT (20). Post et al. reirradiated 50% of the patients with CFRT, 18% with HFRT, and 32% with SRT and reported a median OS time of 9.7 months for all patients, with no difference between the treatment groups (10, 7.7, and 9.7 months, respectively) (18). In a prospective study by Navrarria et al., 2 patients underwent irradiation by SRT (25 Gy/1 fraction), 15 patients by HSRT (37.5 Gy/5 fractions), and 73 patients by CFRT (49.5 Gy/15 fractions). The median OS time and 1-year OS rate were 12 months and 46.7% with HFRT and 18 months and 69.9% with CFRT, respectively (p=0.041) (15). In our study, dose fractionation schemes were not identified as a prognostic factor affecting survival. However, the RT

Table IV: Summary of Selected Reirradiation Studies and Their Results

Authors	N	Histopathology	Dose fraction schedule in reirradiation	Prognostic factors (multivariate analysis)	Survival	RN
Combs et al., 2013 (6)	233	LGG HGG GBM	36 Gy/18 fr	Grade at recurrence, age, RT interval	mOS 8 (GBM), 20 (HGG), 24 (LGG) months	NS
Combs et al., 2018 (7)	565	LGG HGG GBM	15 Gy/1 fr 36 (20-70)/1.2-6.25 Gy	Age, KPS, PTV	mOS 7.5 (GBM), 9.5 (HGG), 13.8 (LGG) months	NS
Shen et al., 2018 (21)	118	HGG	30-50/1.5-2 Gy	RT interval, reirradiation dose, re-resection status	mOS 9.6 months	3.4%
Klobukowski et al., 2018 (12)	82	HGG	35 Gy/10 fr	RT interval, performance status, focality of recurrent tumor, reirradiation dose	mOS 9.5 months	4%
Post et al., 2019 (18)	121	LGG HGG GBM	CFRT HFRT SRT	KPS, grade at recurrence, RT interval, PTV, reirradiation at first relapse	mOS 9.7 months	7.7%
Lee et al., 2016 (13)	36	LGG HGG GBM	CFRT	KPS, RT interval	mOS 11 months 1-year OS 41.7%	14%
Navarria et al., 2019 (14)	300	LGG HGG	CFRT HFRT SRT	Age, grade at recurrence, KPS, RT interval, reirradiation dose	mOS 9.7 months 1-year OS 41% 2-years OS 17.7%	0.3%
Navarria et al., 2022 (15)	90	HGG	25 Gy/1 fr 37.5 Gy/5 fr 49.5 Gy/15 fr	Age, grade at recurrence, RT interval, IDH	mOS 17 months 1-year OS 66.7% 2-years OS 32.6%	10%
Gupta et al., 2021 (8)	111	HGG	54 Gy/27 fr	KPS	1-year OS 61.8%	12%

RN: *Radionecrosis,* ***GBM:*** *Glioblastoma,* ***HGG:*** *High-grade glioma,* ***LGG:*** *Low-grade glioma,* ***CFRT:*** *Conventional fractionated radiotherapy,* ***HSRT:*** *Hypofractionated stereotactic radiotherapy,* ***SRT:*** *Stereotactic radiotherapy,* ***PTV:*** *Planning target volume,* ***KPS:*** *Karnofsky performance status,* ***mOS:*** *Median overall survival,* ***OS:*** *Overall survival,* ***fr:*** *fraction,* ***NS:*** *not defined.*

technique used for reirradiation (3DCRT vs. IMRT vs. VMAT) was associated with survival in univariate analysis. Patients irradiated with VMAT showed better survival outcomes.

One of the most important issues in reirradiation is the dose of RT that can be given. RT doses over certain cut-off values have been reported to improve survival outcomes (8,12-15,18-21). Better survival was reported by Shen et al. at reirradiation doses of >41.4 Gy, Klobukowski et al. at ≥35 Gy, Lee et al. at >45 Gy, Navarria et al. at BED_{10} >43 Gy, and Gupta et al. at 54 Gy (8,12-14,21). In addition, Gupta et al. reported that a cumulative EQD_2 above 104.3 Gy was associated with improved survival in univariate analysis (8). In contrast, Kazmi et al. observed no dose-response relationship in their meta-analysis of patients with reirradiated glioblastoma when the patients were stratified according to a dose of 36 Gy (EQD_2) (10). In our study, we did not determine a reirradiation dose cut-off value associated with survival. However, weak negative correlations were observed between survival and cumulative tumor dose and cumulative BED_{10}. Unlike the above studies, a high cumulative tumor dose (EQD_2 ≥110 Gy) and high cumulative BED_{10} (BED_{10} ≥130 Gy) were found to adversely impact survival. Especially in patients who received a dose of 60 Gy in initial RT, receiving a dose greater than 50 Gy EQD_2 in reirradiation negatively affected survival (median OS 8 vs. 11 months). This raised the question of whether the reduced survival of patients receiving high cumulative radiation doses may be associated with the increased adverse effects of RT. However, we detected no statistically significant relationship between high cumulative dose and radionecrosis. In addition, there were no significant differences in median cumulative EQD_2 and BED_{10} values between the groups with and without radionecrosis. Although high doses may be a criterion for increasing tumor control, they are also the main cause of radionecrosis. However, the risk of radionecrosis may also increase because of reasons other than radiation dose (e.g., dose fractionation scheme, tumor volume). When radionecrosis was ruled out as the cause of poorer survival at higher cumulative doses, no other explanation could be found. However, most patients who received high doses and had worse survival outcomes were patients with high-grade

glioma or glioblastoma at initial irradiation. This may have contributed to their poorer survival.

PTV is the main parameter in the selection of treatment fractionation. The ability to select more ablative schemes such as SRT or HSRT for small-volume tumors increases the local control of these tumors (6,21). With large tumors, critical organs usually do not allow the delivery of a high RT dose to the tumor. Thus, most studies have demonstrated better survival with small tumors (6,21). PTV may affect survival because it has an important role in tumor control. However, studies have yielded different data regarding what PTV values lead to poorer survival. Combs et al. and Shen et al. determined that survival decreased at PTVs greater than 47 mL and 200 cm^3, respectively (6,21). Chapman et al. examined the outcomes of 116 patients with recurrent high grade glial tumors who underwent re-irradiation. They showed that PTV volume >6.4 cc in patients with SRS and >131 cc in patients without SRS negatively affected OS (4). In contrast to the above studies, survival outcomes were affected in patients with much smaller tumor volume (<4.5 cm^3). A survival advantage was observed only with very small tumors.

Combination therapies are often used in recurrent malignant gliomas because the treatment options are unlikely to be successful when applied alone. In a study by Klobukowski et al., the addition of systemic chemotherapy to reirradiation improved survival in univariate analysis. However, concurrent chemotherapy was not found to affect survival in this study (12). Shi et al. analyzed the data of 637 patients in the RTOG 0525 study and reported that the median OS was 8.2 months with reirradiation alone, 10.5 months with chemotherapy, and 12.2 months with reirradiation and chemotherapy, with no significant difference between reirradiation alone and combined reirradiation and chemotherapy (22). Some studies also suggested that the combination of surgery and reirradiation had no effect on survival (6,18,13). In our study, the addition of re-resection and consecutive or concurrent chemotherapy to reirradiation did not alter survival outcomes.

When selecting patients to undergo reirradiation, identifying patients with good prognosis is important to achieve better results. However, when the results of all reirradiated patients are examined, studies indicate that a median OS of approximately 8-17 months can be obtained, with 1-year OS rates up to 60% and 2-year OS results up to 30% (Table IV). Similar to previous research, in our study the median OS of all patients was 11 months and the 1- and 2- year OS rates were 48% and 22%, respectively.

Radionecrosis was the most troubling adverse effect of reirradiation. The dose fractionation scheme used was found to be significant in terms of the development of radionecrosis (15,18,20,21). Shanker et al. observed a significant relationship between radionecrosis and treatment technique after correcting for age, reirradiation BED, RT interval, and treatment volume. Radionecrosis was observed at a rate of 7.1% after HSRT, 6.1% after SRT, and 1.1% after CFRT (20). Post et al. reported no difference between the groups when they compared radionecrosis rates in CFRT, SRT, and HSRT (18). Table IV shows the rates of radionecrosis observed in some studies. The relatively high prevalence of radionecrosis in our study (25%) may be attributable to the fact that the study was multicenter and radionecrosis was often diagnosed radiologically. When factors contributing to the occurrence of radionecrosis were examined, only re-resection was associated with a significantly higher rate of radionecrosis (37.7% vs. 18%). No correlation was detected between the dose fractionation scheme and radionecrosis. The rate of radionecrosis was 28% with SRT, 25% with CFRT, and 20% with HSRT, respectively. In addition, median cumulative EQD_2, cumulative BED_{10}, and tumor volume values did not differ significantly when compared between patients with and without radionecrosis.

Limitations of this study include its retrospective design and our inability to evaluate the tumors in terms of molecular features (e.g., MGMT, IDH). Studies of reirradiated malignant gliomas have yielded different results, especially regarding the relationship between survival and tumor volume and reirradiation dose. We believe that our study can shed some light on these issues because it is based on multicenter data and includes a relatively large sample of patients.

CONCLUSION

In the present study, the median OS time was 11 months and the 1-year and 2-year OS rates were 48% and 22%, respectively. The most important prognostic factors in these patients were performance status, tumor histopathology, and tumor volume. Unlike other studies, our results suggest that high cumulative radiation doses may adversely affect survival outcomes. We also observed that re-resection was associated with a higher risk of radionecrosis. It should be kept in mind that patients planned to receive high doses of re-irradiation may have poorer survival and those undergoing re-resection may have a higher risk of radionecrosis.

Declarations

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AUTHORSHIP CONTRIBUTION

Study conception and design: BY, DA, GY, YG, PE, OC, FIK, CE, NI, EE

Data collection: BY

Analysis and interpretation of results: BY

Draft manuscript preparation: BY

Critical revision of the article: BY, DA, GY, YG, PE, OC, FIK, CE, NI, EE

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