



Hypofractionated Re-irradiation after Maximal Surgical Resection for Recurrent Glioblastoma: Therapeutic Adequacy and Its Prognosticators of Survival

Jeongshim Lee^{1,2}, Sung Soo Ahn³, Jong Hee Chang⁴, and Chang-Ok Suh¹

Departments of ¹Radiation Oncology, ³Radiology, and ⁴Neurosurgery, Yonsei University College of Medicine, Seoul;
²Department of Radiation Oncology, Inha University Hospital, Incheon, Korea.

Purpose: To evaluate the adequacy of retreatment, including hypofractionated re-irradiation (HFReRT), after surgery for recurrent glioblastoma (GBM) and related prognosticators of outcomes.

Materials and Methods: From 2011 to 2014, 25 consecutive patients with recurrent (n=17) or secondary (n=7) disease underwent maximal surgery and subsequent HFReRT after meeting the following conditions: 1) confirmation of recurrent or secondary GBM after salvage surgery; 2) Karnofsky performance score (KPS) ≥ 60 ; and 3) interval of ≥ 12 months between initial radiotherapy and HFReRT. HFReRT was delivered using a simultaneous integrated boost technique, with total dose of 45 Gy in 15 fractions to the gross tumor volume (GTV) and 37.5 Gy in 15 fractions to the clinical target volume.

Results: During a median follow-up of 13 months, the median progression-free and overall survival (OS) were 13 and 16 months, respectively. A better KPS ($p=0.026$), no involvement of the eloquent area at recurrence ($p=0.030$), and a smaller GTV ($p=0.005$) were associated with better OS. Additionally, OS differed significantly between risk groups stratified by the National Institutes of Health Recurrent GBM Scale (low-risk vs. high-risk, $p=0.025$). Radiologically suspected radiation necrosis (RN) was observed in 16 patients (64%) at a median of 9 months after HFReRT, and 8 patients developed grade 3 RN requiring hospitalization.

Conclusion: HFReRT after maximal surgery prolonged survival in selected patients with recurrent GBM, especially those with small-sized recurrences in non-eloquent areas and good performance.

Key Words: Recurrent glioblastoma, retreatment, re-irradiation, surgery, survival

INTRODUCTION

Long-term local control of glioblastoma (GBM) is rarely achieved with standard treatments, which include maximal surgical resection followed by radiotherapy (RT) with concomitant

and adjuvant temozolomide. Such cases nearly always experience a relapse within 5 years.¹⁻⁵ Although a standard of care has not been established for recurrent GBM, various re-treatment approaches, including re-operation, re-irradiation, chemotherapy (CTx), and combined treatment, are used despite the increased risks of toxicity and uncertainty regarding survival advantages.⁶

Although re-operation is an effective option for patients with small tumor volumes, good Karnofsky performance scores (KPSs), no involvement at the eloquent site, and young ages, this treatment is indicated for only 10–30% of patients with recurrent GBM.⁷⁻¹⁰ Re-irradiation with a moderate dose (~40 Gy) and conventional fractionation has yielded acceptable complication rates; however, the efficacy of this treatment remains undetermined because of the relatively low radiation doses administered to GBMs. Recently, hypofractionated RT administered via intensity modulated RT (IMRT) and/or stereotactic RT has improved the outcomes of re-irradiation for recurrent

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Co-corresponding authors: Dr. Chang-Ok Suh, Department of Radiation Oncology, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.

Tel: 82-2-2228-8117, Fax: 82-2-312-9033, E-mail: cosuh317@yuhs.ac and Dr. Jong Hee Chang, Department of Neurosurgery, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
Tel: 82-2-2228-2162, Fax: 82-2-393-9979, E-mail: changjh@yuhs.ac

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GBM.¹¹⁻¹⁴ However, almost all treated patients, particularly those treated with stereotactic radiosurgery (SRS), experienced recurrent GBMs with small volumes that could not be differentiated from treatment-related changes, pseudoprogression, or radiation necrosis (RN).¹⁵ Therefore, a recurrence should be pathologically confirmed before subjecting patients with recurrent GBM to salvage treatment.

In light of these earlier findings, our institution administers hypofractionated re-irradiation (HFRtRT) to patients with recurrent GBM who had undergone maximal surgical resection. We hypothesized that for selected cases of recurrent GBM, this treatment combination likely comprises the most effective salvage treatment and provides the best chance of survival prolongation. In addition, we evaluated the adequacy of HFRtRT after maximal surgical resection in patients with recurrent GBM.

MATERIALS AND METHODS

Study design

We prospectively collected and followed all cases of recurrent or secondary GBM treated with HFRtRT after salvage surgery at our institutions between November 2011 and December 2014. All patients were presented to our institute's multidisciplinary neuro-oncology tumor conference, which included neurosurgeon, radiation oncologist, neuro-oncologist, and neuro-radiologist. Tumor recurrences were identified by the appearance of new contrast-enhanced lesions on T1-weighted magnetic resonance imaging (MRI) scans or increase in the volumes of enhanced lesions that had been recorded as treatment-related changes after initial treatment. Eventually, a diagnosis of recurrent GBM was established via histologic analysis after salvage surgery, and HFRtRT was offered to selected patients who met the following inclusion criteria, based on our previous work: 1) pathologically confirmed recurrent GBM treated with salvage surgery; 2) age of 18–70 years; 3) KPS \geq 60 at the time of referral for HFRtRT; and 4) an interval of \geq 12 months between initial RT and HFRtRT.¹⁶ This study was approved by our Institutional Review Board (4-2017-0878).

Salvage re-treatment

Patients with recurrent or secondary GBM underwent maximal surgical resection of the enhancing lesions identified on MRI scans. HFRtRT was offered to patients within 4 weeks after salvage surgery. Each patient underwent a computed tomography simulation in the supine position while immobilized with a customized thermoplastic mask device. MRI scans at recurrence and after salvage surgery for the recurrent tumor were transferred to the planning system; after image fusion, the gross tumor volume (GTV) was delineated on T1-weighted MRI scans, based on the operative cavity and residual contrast (gadolinium)-enhanced lesion plus a 0.5-cm margin. The

clinical target volume (CTV) was defined as the GTV with a 1–2-cm expansion to account for peritumoral edema on T2 fluid-attenuated inversion recovery MRI sequences. HFRtRT was delivered via helical tomotherapy with 6-MV photons (Tomotherapy, Madison, WI, USA) using a simultaneous integrated boost technique. Doses of 45 Gy in 15 fractions and 37.5 Gy in 15 fractions were delivered to the GTV and CTV, respectively.

Treatment outcomes and prognostic variables

All patients underwent MRI evaluations at 1 month after salvage treatment for recurrent GBM, and every 3 months thereafter. During follow-up, the treatment outcome and toxicity assessments included a thorough history taking, physical examination (particularly the KPS and neurological status), and analysis of all available imaging data, including contrast-enhanced brain MRI scans. Toxicity after salvage treatment was assessed according to the criteria of the Radiation Therapy Oncology Group. However, no specific tool was used to assess the patients' neurocognitive status or quality of life. The primary endpoints for analysis were overall survival (OS) and progression-free survival (PFS). OS was calculated from the date of surgery for recurrence to the date of death from any cause, and PFS was measured from the date of recurrence until the date of tumor progression or death. The following prognostic factors associated with OS were included: age, gender, KPS, initial histology, eloquent area involvement at recurrence, extent of surgery at recurrence, O6-methylguanine-DNA-methyltransferase status at recurrence, isocitrate dehydrogenase (IDH) mutation at recurrence, tumor volume at recurrence, GTV for HFRtRT, and interval between RT courses. In addition, we divided patients into prognostic groups using the NIH recurrent GBM scale, which is a practical scoring system devised by the National Institutes of Health (NIH),⁹ and assessed OS by group. The secondary endpoints included any documented treatment-related toxicity observed during follow-up examinations and on MRI scans.

Statistical analysis

Survival rates were estimated using the Kaplan-Meier method. A univariate analysis of risk factors was performed by comparing survival rates using the log-rank test. A multivariate analysis was performed using a Cox regression model with a stepwise method to identify prognostic factors. A *p* value $<$ 0.05 was considered statistically significant. All analyses were performed using IBM SPSS, version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient and treatment characteristics

Our study population included 25 patients (11 men, 14 women) with a median age at recurrence of 45 years (range, 23–61 years) and median and minimum KPSs of 90 and 60, respec-

tively. Among all patients, 8 patients had secondary GBM, who were initially diagnosed with WHO grade II/III glioma. The median recurrent tumor volume was 32 mL (range, 4–90 mL). All patients underwent surgery for pathologic diagnosis and maximal tumor debulking; 15 underwent gross total resection (GTR) and 10 underwent subtotal resection, defined as the removal of >90% of the contrast-enhanced tumor. All patients had received a median postoperative RT dose of 60 Gy (range, 54–70 Gy) at the time of the initial diagnosis, and the median time interval between the initial RT and re-irradi-

ation courses was 30 months (range, 12–72 months; 29 months for primary recurrent GBM, 30 months for secondary GBM). At the time of HFRtRT, the median GTV and CTV were 97 mL (range, 21–261 mL) and 270 mL (range, 101–1353 mL), respectively. Thirteen patients received sequential systemic therapy with temozolomide after HFRtRT. Details of the baseline characteristics are described in Table 1.

Survival and prognostic variables

Patients were followed up for a median of 13 months (range,

Table 1. Patient and Treatment Characteristics

Characteristic	All patients (n = 25)	
		n (%)
Age (yr)	Median (range)	45 (23–61)
	<45	10 (40)
	≥45	15 (60)
Sex	Male	11 (44)
	Female	14 (56)
Initial histology	WHO II glioma	2 (8)
	WHO III glioma	6 (24)
	GBM	17 (68)
Initial RT dose (Gy)	Median (range)	60 (54–70)
Initial CTx	No	7 (28)
	Yes	18 (72)
KPS at recurrence	Median (range)	90 (60–100)
Eloquent area involvement at recurrence	No	13 (52)
	Yes	12 (48)
Extent of surgery at recurrence	Gross total	15 (58)
	Subtotal	10 (42)
MGMT status at recurrence	Unmethylated	9 (36)
	Methylated	16 (64)
IDH mutation at recurrence	Present	8 (32)
	Absent	14 (56)
	Unknown	3 (12)
Tumor volume at recurrence (mL)*	Median (range)	32 (4–90)
	<50	15 (60)
	≥50	10 (40)
GTV of HFRtRT (mL)	Median (range)	97 (21–261)
	<100	14 (56)
	≥100	11 (44)
CTV of HFRtRT (mL)	Median (range)	270 (101–1353)
CTx after HFRtRT	No	12 (48)
	Yes, sequential	13 (52)
Cumulative dose of RT (Gy)	Median (range)	105 (95.4–115)
	<100	2 (8)
	≥100	23 (92)
Interval between RT (month)	Median (range)	29 (12–72)
	<30	13 (52)
	≥30	12 (48)

WHO, World Health Organization; GBM, glioblastoma; RT, radiotherapy; KPS, Karnofsky performance score; MGMT, O6-methylguanine-DNA-methyltransferase; IDH, isocitrate dehydrogenase; GTV, gross tumor volume; CTV, clinical target volume; HFRtRT, hypofractionated re-irradiation; CTx, chemotherapy.

*Classified using a tumor volume cut-off value of 50 mL at recurrence, according to the National Institutes of Health recurrent GBM scale.

4–41 months) after a recurrence. At the time of the last observation, 5 patients (20%) remained alive at 15, 16, 22, 28, and 29 months after recurrence; the other 20 (80%) had died. The me-

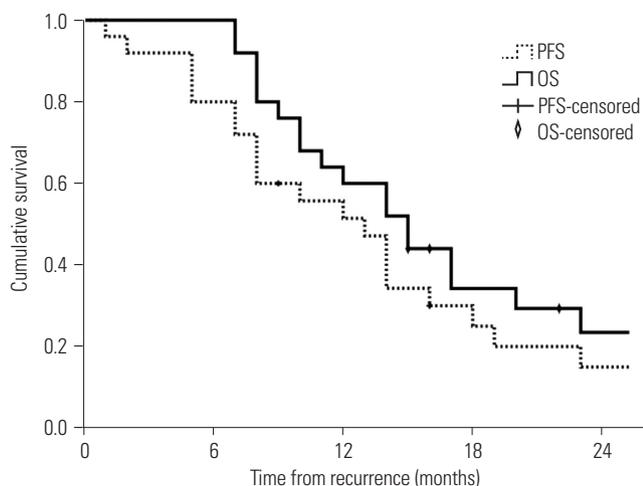
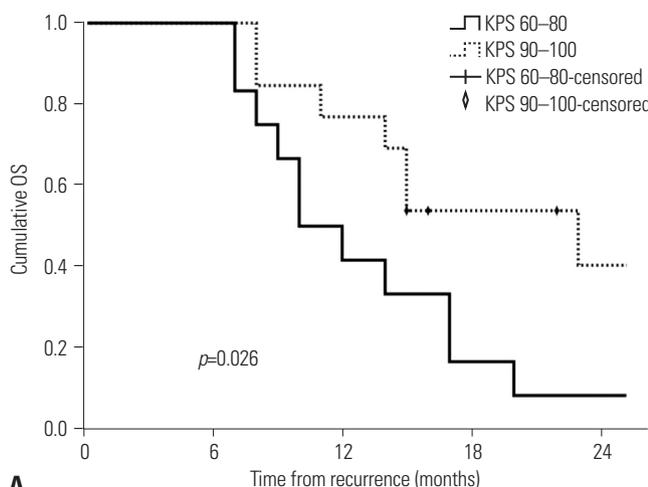
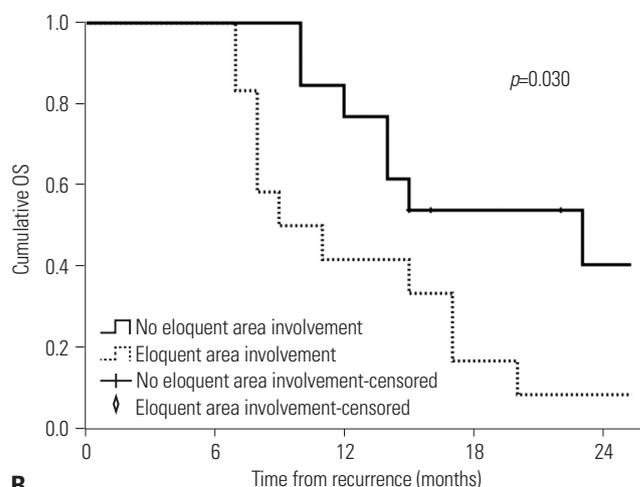


Fig. 1. Kaplan-Meier curves of PFS and OS. PFS, progression-free survival; OS, overall survival.

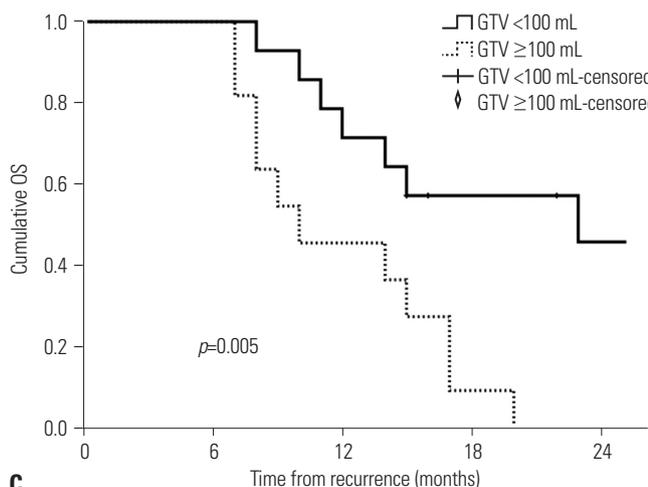
dian PFS duration and 1-year PFS rate were 13 months (range, 1–41 months) and 51.4%, respectively, and the median OS duration and 1-year OS rate were 16 months (range, 7–41 months) and 60%, respectively (Fig. 1). A univariate analysis of factors related to OS after a recurrence identified the KPS ($p=0.026$) (Fig. 2A), eloquent area involvement at recurrence ($p=0.030$) (Fig. 2B), GTV at HFRerT ($p=0.005$) (Fig. 2C), and administration of sequential CTx after HFRerT ($p=0.033$) (Fig. 2D) as significant factors. In contrast, age ($p=0.385$), initial histology ($p=0.232$), the extent of surgery at recurrence ($p=0.391$), IDH mutation status at recurrence ($p=0.626$), tumor volume at recurrence ($p=0.075$), and interval between RT ($p=0.489$) did not affect OS. All results from the univariate analysis are shown in Table 2. In a multivariate stepwise Cox regression model analysis, the GTV at HFRerT (≥ 100 mL vs. < 100 mL: hazard ratio=3.717, 95% confidence interval: 1.356–10.187, $p=0.011$) was confirmed as an independent prognostic factor affecting OS (Table 2).



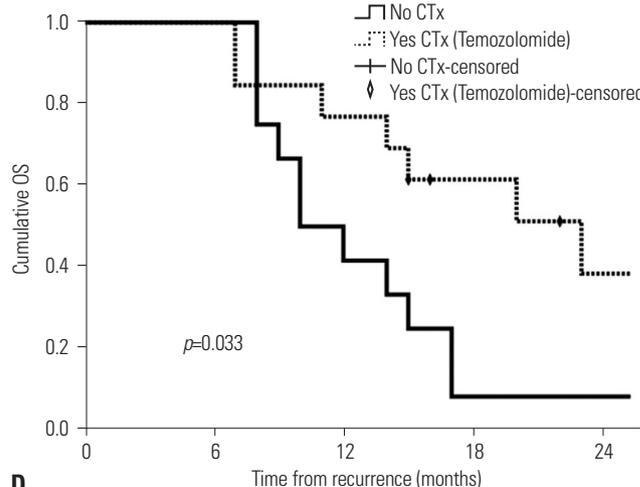
A



B



C



D

Fig. 2. OS according to the KPS (A), eloquent area involvement at recurrence (B), GTV (C), and CTx after hypofractionated re-irradiation (D). OS, overall survival; KPS, Karnofsky performance score; GTV, gross tumor volume; CTx, chemotherapy.

Survival according to prognostic groups as defined by the NIH recurrent GBM scale

We classified patients into prognostic groups based on the NIH recurrent GBM scale, which included the involvement of eloquent regions, KPS ≤ 80 , and recurrent tumor volume ≥ 50 mL.⁹ Because our cohort was small, we defined the following groups: NIH recurrent GBM scale of 0 or 1 (low-risk group, n=14) and NIH recurrent GBM scale of 2 or 3 (high-risk group, n=11). The NIH recurrent GBM scale was found to be a significant prognosticator of OS (low-risk group vs. high-risk group: 15 months vs. 10 months, $p=0.025$) (Fig. 3).

Toxicity

During treatment, no severe acute toxicity events requiring the interruption of HFReRT were recorded. During the follow-up period, corticosteroids, antiepileptic drugs, and mannitol were administered in 22 (88%), 22 (88%), and 7 (28%) cases, respectively. At a median of 9 months after HFReRT, 16 patients (64%) harbored suspected areas of RN, based on gadolinium-enhanced T1-weighted MRI scans. However, these lesions could not be completely differentiated from tumor progression.

Of these 16 patients, 8 were hospitalized for neurological deterioration with suspected grade 3 RN. Grade 3 RN developed in 18.8% (3/16) of cases involving an interval of >24 months between RT courses and in 55.6% (5/9) of cases with an interval of <24 months ($p=0.062$). No differences in the incidence of grade 3 RN according to GTV and CTV were observed.

DISCUSSION

According to several studies, a more aggressive local treatment comprising GTR and/or high-dose re-irradiation via advanced RT techniques may improve the survival of selected patients with recurrent GBM.^{6,7,13,17,18} However, the use of re-irradiation, which is associated with late side effects and tumoricidal effects, remains controversial. Accordingly, our institution has implemented very strict criteria regarding the administration of HFReRT to patients with recurrent GBM, as we expect that the benefits of salvage HFReRT in terms of increased tumor control would outweigh the costs of treatment-related toxicity.

Table 2. Univariate and Stepwise Multivariate Cox Regression Analyses of Prognosticators of OS

Characteristics	Univariate analysis		Multivariate analysis [†]		
	1-year OS	p value	HR	95% CI	p value
Age (yr)	<45	60.0	0.385	NI	
	≥ 45	60.0			
Sex	Male	63.6	0.565	NI	
	Female	57.1			
KPS	60–80	41.7	0.026*	Ref	0.680
	90–100	76.9		0.759	0.204–2.815
Initial histology	Non-GBM	50.0	0.232	NI	
	GBM	64.7			
Eloquent area involvement at recurrence	No	76.9	0.030*	Ref	0.584
	Yes	41.7		1.381	0.435–4.388
Extent of surgery at recurrence	Gross total	73.3	0.391	NI	
	Subtotal	40.0			
MGMT status at recurrence	Unmethylated	55.6	0.978	NI	
	Methylated	62.5			
IDH mutation at recurrence	Present	62.5	0.626	NI	
	Absent	57.1			
Tumor volume at recurrence (mL)	<50	73.3	0.075	NI	
	≥ 50	40.0			
GTV of HFReRT (mL)	<100	71.4	0.005*	Ref	0.011
	≥ 100	45.5		3.717	1.356–10.187
Interval between RT (month)	<30	61.5	0.489	NI	
	≥ 30	58.3			
Sequential CTx after HFReRT	No	41.7	0.033*	Ref	0.231
	Yes, Temozolomide	76.9		0.528	0.185–1.503

OS, overall survival; HR, hazard ratio; CI, confidence interval; KPS, Karnofsky performance score; GBM, glioblastoma; MGMT, O6-methylguanine-DNA-methyltransferase; IDH, isocitrate dehydrogenase; GTV, gross tumor volume; HFReRT, hypofractionated re-irradiation; RT, radiotherapy; CTx, chemotherapy; Ref, reference; NI, not included.

*Included in the multivariate analysis, [†]Variables with a p value ≤ 0.05 were entered in the multivariate regression model in a stepwise manner and were removed at any point if the p value exceeded 0.05.

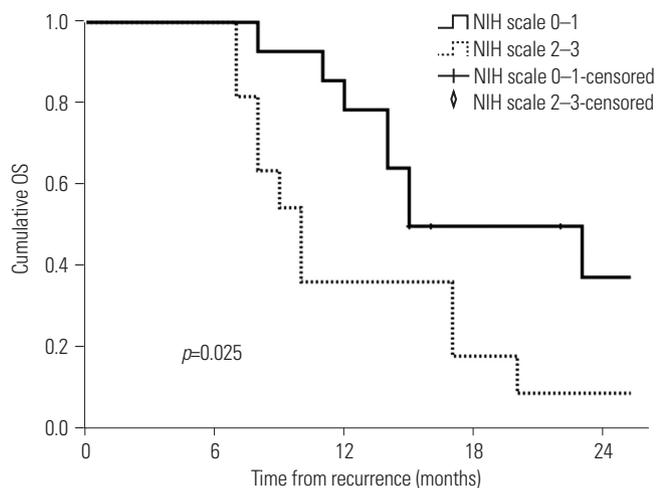


Fig. 3. OS according to prognostic groups, defined according to the NIH recurrent glioblastoma scale. OS, overall survival; NIH, National Institutes of Health.

Given the uncertainty of a differential diagnosis that includes both recurrent GBM and treatment-related lesions such as pseudoprogression or RN after initial treatment for malignant gliomas,¹⁹ we applied HFRt only to patients with pathologically confirmed recurrent or secondary GBM. Previous re-irradiation series involving patients with non-pathologically confirmed recurrent GBM, especially those treated with SRS, might have included cases of treatment-related reactions rather than true GBM, which might have led to overestimations of the outcomes.^{6,13,15,20-23} Next, our study required the total or subtotal removal of all suspected recurrent GBMs with the aim of maximum debulking prior to HFRt, which would thus improve the efficacy of this treatment given the radio-resistance of recurrent tumors and uncontrolled behaviors of bulky gross tumors in response to radiation.^{6,7,24,25} Notably, the extent of surgery did not affect survival in the current study, despite previous reports that the extent of resection is a well-known predictive factor for survival.^{24,25} This discrepancy may be attributable not only to the limited number of patients, but also to the fact that upfront HFRt (i.e., within 4 weeks after salvage re-operation) may have temporarily controlled the small amount of residual tumor remaining after subtotal removal, which we defined as the resection of >90% of a tumor.²⁵

The performance status has also been identified as a factor affecting the use of HFRt in patients with recurrent GBM. Several studies have reported strong correlations between a good performance score and longer survival.¹⁶ Given the fundamental importance of this factor, particularly in a re-treatment setting, we set a poor KPS (<60) as an exclusion criterion to reduce the risks of physical and neurological deterioration after treatment. Notably, a higher performance status, no eloquent area involvement, and a smaller GTV were identified as positive prognostic factors related to OS in the selected patients who received HFRt following surgical resection. These prognosticators were similar to those used in the abovementioned

validated NIH scale to predict outcomes after the surgical resection of recurrent GBM.⁹ The difference in tumor volumes between the studies (GTV=100 mL vs. tumor volume at recurrence=50 mL) was a consequence of the time points used to determine the treatment modalities (postoperative status vs. preoperative status). Both studies also proposed that the subgroup of patients with a poor performance and large or diffuse recurrent tumors located in the eloquent brain area might benefit from best supportive care, rather than re-treatment.

Regarding dose fractionation in the context of re-irradiation, the prescribed doses in a recent review ranged from 20 Gy to 45.5 Gy, and the cumulative equivalent radiation doses (in 2-Gy fractions; EQD2) for both primary and second RT ranged from 81.6 Gy to 102.8 Gy.²⁶ In most published studies, the doses prescribed for re-irradiation ranged from 30 Gy to 45 Gy, thus maintaining a cumulative EQD2 of approximately 100 Gy. More recently, however, advances in conformal radiation techniques, such as stereotactic RT and IMRT, have led to the delivery of higher therapeutic re-irradiation doses via hypofractionation within short treatment courses.²⁶ In such situations, we prescribed 45 Gy in 15 fractions (EQD2, 56.25 Gy) to the operative cavity with/without gross residual tumors plus 0.5 cm. This was expected to reduce the treatment period along with the tumoricidal re-irradiation dose, as most patients with recurrent GBM have a short life expectancy, limited mobility, and considerable dependency.

Studies of surgery or conventional RT for recurrent GBM have reported mild or moderate survival benefits. Although most studies of surgery for recurrences were affected by a high probability of selection bias, the reported median intervals from salvage surgery to death remained <12 months,^{9,10} and the survival durations of patients treated with conventional re-irradiation for recurrent glioma were also <12 months.^{16,21} In the present study, HFRt after maximal resection yielded a median survival duration of 16 months, although the follow-up period was short. We attribute these outcomes to a synergistic effect for the following reasons: 1) maximal surgical resection is the best approach for tumor eradication and 2) compared to conventional RT, higher RT dose with a precision technique was applied in our HFRt strategy.

We additionally evaluated the safety of HFRt after surgical resection for recurrent GBM. No acute toxicity events were recorded during HFRt, and all patients completed treatment during a median period of 20 days. However, 16 (64%) patients developed late toxicities, including 8 cases each of grade 2 and grade 3 RN. This considerably high incidence of RN in our study, relative to other studies,²⁶ could not completely be attributed to tumor progression. Re-irradiation is a well-known factor that contributes to the risk of RN in cases receiving a cumulative total irradiated dose of >100 Gy, a larger irradiated volume, and a higher fractional dose, as well as those involving a short interval between RT courses.^{27,28} Overall, our study cases exhibited the following risk factors: a median

HFRERT GTV of 97 mL, median CTV of 270 mL, high median cumulative dose of 105 mL, and high fraction dose of 3 Gy. These results suggest that clinical feasibility of the current re-treatment protocol should be investigated based on the clear evidence indicating late toxicity.

Despite large treated volumes, the current treatment scheme encouragingly prolonged survival in our cohort of selected patients with recurrent GBM, which was relatively homogeneous regarding demographic and treatment characteristics. However, we did not address the meaningful benefit of re-treatment in patients with recurrent GBM in terms of the negative effects of treatment-related toxicity on the quality of life or the caregivers' burdens during the end-of-life phase.²⁹ Re-treatment for recurrent GBM should always be considered after thoroughly discussing the potential advantages and disadvantages with patients and their family.

We note that our current study was limited by a small cohort and the risk of selection bias. Furthermore, our study featured some flaws in patient composition. Our cohort comprised of patients with both secondary and recurrent GBM, which are different diseases; Secondary GBM might have better survival outcome. Additionally, our study lacked a comprehensive assessment of toxicity after re-treatment. The retrospective design precluded our ability to evaluate the quality of life, including systemic neurocognitive function, of patients in our cohort. Accordingly, our findings must be validated in well-designed studies with larger cohorts.

In conclusion, the combined use of HFRERT with maximal surgical resection has prolonged the survival of selected patients with recurrent GBM. This re-treatment strategy was especially beneficial for patients with smaller-sized recurrent GBMs, no eloquent area involvement, and good performance scores. However, studies with larger numbers of patients are needed to determine the efficacy of this treatment scheme in light of the significant risk of RN.

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ORCID

Jeongshim Lee <https://orcid.org/0000-0002-7280-5401>
 Jong Hee Chang <https://orcid.org/0000-0003-1509-9800>
 Chang-Ok Suh <https://orcid.org/0000-0002-3375-7072>

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