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ORIGINAL ARTICLE

Optimal clinicogenetic criteria for post-operative re-irradiation in recurrent glioblastoma: KROG 21-02

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Background: Patients with glioblastoma (GBM) often have disease progression after standard temozolomide-based chemoradiation. The benefits and optimal use of re-irradiation (re-RT) following re-operation (re-OP) in recurrent GBM (rGBM) remain uncertain. In this study, we assessed the efficacy and safety of post-operative re-RT in patients with isocitrate dehydrogenase—wild-type rGBM, aiming to identify survival benefits and determine clinicogenetic criteria for patient selection.

Patients and methods: Data from the Korean Radiation Oncology Group 21-02 retrospective study were evaluated, including 531 patients with rGBM from 2013 to 2019. A subset of 164 patients undergoing re-OP were analyzed for survival and benefits of post-operative re-RT. Additionally, 206 patients receiving re-RT, irrespective of re-OP, were evaluated for risks of radiation necrosis. The overall survival (OS) after re-OP was the primary endpoint. Statistical analyses included the Kaplan—Meier method and log-rank test for OS, Cox proportional hazards regression model for univariate and multivariate analyses, and the Fine—Gray competing risk model for assessing the risk of brain necrosis.

Results: The median OS after re-OP was 13.4 months. Kaplan—Meier analysis revealed significantly better OS for those who received re-RT (17.6 months) than for those who did not (11.0 months; $P = 0.002$). Factors associated with improved OS included higher Karnofsky performance status scores, post-operative re-RT, and additional systemic therapy after re-OP. Factors associated with adverse outcomes included recurrence outside the initial RT field and homozygous deletion of CDKN2A/B. The incidence of grade 2 or higher RT necrosis was 5.8% among those undergoing both re-OP and post-operative re-RT.

Conclusion: Post-operative re-RT appears to be associated with enhanced survival and minimal toxicity in patients with rGBM following temozolomide chemoradiation. Our study suggests a novel clinicogenetic criterion for re-RT after re-OP in rGBM, which requires further validation.

Key words: biomarker, radiation necrosis, radiotherapy, recurrent glioblastoma, re-irradiation

INTRODUCTION

Glioblastoma (GBM) is the most prevalent and aggressive malignant brain tumor in adults.[1] The standard treatment for newly diagnosed GBM includes maximal surgical resection, followed by concurrent and adjuvant temozolomide with radiotherapy (RT).[2-4] Despite multimodal treatment approaches, GBM prognosis remains poor, with most patients experiencing disease recurrence.[5] In recurrent disease, the median survival period remains notably short, estimated at 2.9-18.3 months.[6] Unlike initial standard treatments, there is no established standard therapeutic approach for recurrent GBM (rGBM), leading to the use of

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various approaches, such as re-operation (re-OP), re-irradiation (re-RT), and chemotherapy.[7,8]

Previous studies have demonstrated that repeated surgical resection, when feasible, is an effective therapeutic approach to enhance survival in rGBM.[9-12] Similar to the initial treatments, the administration of post-operative re-RT following re-OP may improve tumor control.[13,14] Nevertheless, unlike initial treatments, the use of re-RT is frequently constrained by the risk of RT necrosis, a consequence of the elevated cumulative doses delivered during initial standard chemoradiation.[15] Post-operative re-RT is frequently advised for patients after a re-OP, but well-defined criteria for its use remain elusive. Current general guidelines recommend delaying re-RT for a minimum of 6 months following prior RT.[14,16,17] However, the specific patient groups that should be prioritized for re-RT post-reoperation are yet to be clearly defined.

In this study, we aimed to evaluate the survival benefit and toxicity of re-RT in patients who underwent re-OP for rGBM using multicenter data from the Korean Radiation Oncology Group (KROG) 21-02.[18] Additionally, we aimed to establish a novel clinicogenetic criterion for patient selection, including clinical factors and genetic biomarkers, to enhance re-RT survival outcomes following re-OP.

METHODS

Study population

This multicenter retrospective study was approved by the KROG and authorized by the institutional review boards (IRBs) of each participating institution (Severance Hospital IRB approval number: 4-2023-1329). Given the retrospective nature of this study, the requirement for informed consent was waived. The eligibility criteria included the following: (i) confirmed GBM diagnosis between 2013 and 2019, (ii) age over 18 years at the time of diagnosis, (iii) completion of temozolomide-based chemoradiation (total RT dose $\geq$50 Gy), and (iv) disease progression confirmed according to the Response Assessment in Neuro-Oncology criteria.[19] The exclusion criteria were as follows: (i) intracranial RT before GBM diagnosis, (ii) other brain tumors diagnosed before GBM, (iii) death or loss to follow-up without evidence of recurrence, (iv) diffuse midline glioma, and (v) any other malignancy within the past 5 years. A total of 531 patients with rGBM who met the inclusion criteria were identified, of whom 164 patients with isocitrate dehydrogenase—wild-type GBM who underwent re-OP were analyzed for survival. Additionally, 206 patients who underwent re-RT regardless of re-OP were identified, and the risk factors for RT necrosis were analyzed. Further details on the study population selection are provided in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2026.107730. Molecular profiling was used to assess tumor tissue obtained at the time of the initial diagnosis.

Treatment for rGBM

All patients were treated and followed up by a multidisciplinary neuro-oncology team at each institution, reflecting real-world clinical practice. Re-OP decisions were primarily based on each institution's standard protocols, focusing on patients with localized recurrence amenable to maximal safe resection. The neurosurgical teams deemed re-operation feasible if post-operative morbidity was expected to be minimal and if a total or at least subtotal resection could be achieved. In detail, the extent of resection was evaluated using gadolinium-enhanced brain magnetic resonance imaging conducted within 48-72 h. Gross total resection (GTR), defined as >99% removal of the enhancing tumor, was considered a complete resection, whereas 50%-99% removal was classified as a subtotal resection, and <50% removal, as a biopsy. With these criteria, only patients who underwent surgery with at least a subtotal resection were considered for re-OP. Initial progression patterns were defined as in-field, marginal, and out-of-field progression based on >80%, 20%-80%, and <20% of the tumor recurrence volume within the 95% isodose line during initial concurrent chemoradiation, respectively. For re-RT, target volumes were defined using contrast-enhanced T1-weighted magnetic resonance imaging (MRI), with a 5- to 10-mm margin added to generate the clinical target volume and an additional 3-5 mm for the planning target volume, particularly when image guidance was applied. Hypofractionated regimens, typically 40-50 Gy in 10-20 fractions, were commonly used for treatment. Treatment plans were individualized based on these general principles at the discretion of the treating clinician. Detailed dose schemes and techniques are summarized in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2026.107730. Re-RT included only patients who received fractionated external beam RT and excluded those treated with stereotactic radiosurgery or gamma knife surgery. Because histopathological confirmation was not routinely feasible, the diagnosis of RT necrosis was established through multidisciplinary consensus based on a combination of MRI findings (including contrast-enhanced T1-weighted and, when available, perfusion-weighted imaging) and clinical symptoms, consistent with established criteria in the literature.[20-22] RT necrosis associated with re-RT was evaluated using the Common Terminology Criteria for Adverse Events, version 5.0.

Statistical analysis

The primary endpoint of this study was overall survival (OS), which was defined as the duration between re-OP and either death or last follow-up. Progression-free survival (PFS) was also analyzed as a secondary endpoint and was defined as the time from re-OP to either radiographic or clinical progression, or death from any cause. Group comparisons between patients who underwent re-RT and those who did not were carried out using the chi-square test or Fisher's exact test for categorical variables. Student's *t* test or Wilcoxon test was used to analyze continuous variables.

OS and PFS were analyzed using the Kaplan–Meier method, and comparisons between treatment groups were carried out using the log-rank test. Univariate and multivariate analyses were carried out using the Cox proportional hazards regression model. For the multivariable analysis, a backward stepwise regression approach was used, selecting the model with the lowest Akaike information criterion value. The risk of brain necrosis due to re-RT was analyzed using the Fine–Gray competing risk model. Statistical analyses were carried out using the R software version 4.3.3 (The R Foundation, Boston, MA). A significance level of $P < 0.05$ was used for all statistical tests.

RESULTS

Patient characteristics

The median age at diagnosis was 56.7 [interquartile range (IQR) 49.2-62.6] years, and 52.4% of the patients were male. Table 1 presents the characteristics of the patients who underwent re-OP. Among the 164 patients, 82 underwent post-operative re-RT, and 82 did not. In patients who underwent post-operative re-RT, the median total dose was 45 Gy (IQR 30-45 Gy), and the median total number of fractions was 15 (IQR 5-20).

A comparative group analysis showed no significant differences in clinical factors, such as sex, age, Karnofsky performance status (KPS), extent of resection, patterns of recurrence, and genetic biomarkers. An exception was noted in the recurrence interval, in which the post-operative re-RT group demonstrated a significantly longer interval of median 20.8 months (IQR 11.9-32.5 months) compared with median 9.7 months (IQR 5.6-15.3 months) in the group not receiving re-RT. In both groups, the most commonly used post-operative systemic therapy regimen was the reuse of temozolomide (37.8%), followed by other agents such as bevacizumab (9.1%) or procarbazine, lomustine, and vincristine (6.1%), whereas 42.7% of patients did not receive chemotherapy. A detailed breakdown of regimens is presented in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2026.107730.

Survival outcome

The median follow-up duration from re-OP among survivors was 11.7 months (IQR 5.6-32.4). The median OS for all patients who underwent re-OP was 13.4 months (IQR 12.3-17.1). The Kaplan–Meier curves for OS showed a significant difference between those who received post-operative re-RT and those who did not (median OS 17.6 versus 11.0 months, $P = 0.002$; Figure 1A). In the multivariate analysis, a higher KPS [hazard ratio (HR) 0.24, $P = 0.008$], post-operative re-RT (HR 0.16, $P = 0.011$), and post-operative systemic therapy (HR 0.35, $P = 0.028$) were significantly associated with better OS (Table 2). Conversely, recurrence outside the initial field (HR 4.72, $P = 0.002$) and the presence of a *CDKN2A/B* homozygous deletion (HR 5.24, $P = 0.010$) were associated with a worse prognosis. Upon investigating the relationships among *MGMT* methylation, *EGFR* amplification, *CDKN2A/B* homozygous deletion, *TERT* promoter mutation, and *TP53* mutation, all factors had a variance inflation factor of less than three, indicating no significant correlations between them. Further results on OS according to specific post-operative systemic therapy regimens are presented in Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2026.107730.

The median PFS for the entire cohort was 6.8 months (IQR 3.5-11.5). Patients who received post-operative re-RT had a significantly longer median PFS compared with those who did not (median PFS 7.3 versus 6.0 months, $P = 0.011$; Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2026.107730). In the multivariate Cox regression analysis (Supplementary Table S3), post-operative re-RT remained independently associated with improved PFS (HR 0.24, $P = 0.013$), along with other significant factors such as extent of resection (HR 15.41, $P < 0.001$), CDKN2A/B homozygous deletion (HR 5.01, $P = 0.006$), and post-operative systemic therapy (HR 0.27, $P = 0.003$). Further details on PFS according to specific post-operative systemic therapy regimens are provided in Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2026.107730.

Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2026.107730, presents the analysis results of prognostic factors for OS among patients who underwent post-operative re-RT ($n = 82$). In the multivariate analysis, a higher KPS (HR 0.39, $P = 0.003$) and longer recurrence interval (HR 0.23, $P < 0.001$) were identified as favorable prognostic factors, whereas incomplete resection (HR 2.31, $P = 0.006$) and recurrence outside the initial field (HR 2.11, $P = 0.012$), distinct from previously treated areas, were associated with poor prognosis. For PFS, as shown in Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2026.107730, favorable factors included higher KPS (HR 0.36, $P = 0.002$), longer recurrence interval (HR 0.48, $P = 0.015$), and post-operative systemic therapy (HR 0.48, $P = 0.005$), whereas incomplete resection (HR 2.01, $P = 0.013$) and recurrence outside the initial field (HR 3.18, $P < 0.001$) were associated with worse PFS.

Subgroup analysis

To identify patients who could benefit from post-operative re-RT, a subgroup analysis was carried out. Figure 2 illustrates forest plots for each subgroup. Post-operative re-RT benefited patients with a recurrence interval of $\geq$12 months and potentially those with a *TERT* promoter mutation, *CDKN2A/B* deletion, or higher KPS, although the latter results lacked statistical significance, owing to the small sample sizes. Although statistical significance for interactions within subgroups in the forest plot analysis was observed only for recurrence interval, a risk-group-adapted approach was adopted by including the top four factors that demonstrated the greatest differences in post-operative re-RT benefit within the subgroups: recurrence

Table 1. Characteristics of patients who underwent re-operation

Characteristics	Re-RT (*n* = 82)		No re-RT (*n* = 82)		Total (*n* = 164)		*P* value
Sex							
Male	38	46.3%	48	58.5%	86	52.4%	0.159
Female	44	53.7%	34	41.5%	78	47.6%	
Age, median (IQR)	54.2 (47.5-61.4)		57.6 (50.5-63.7)		56.7 (49.2-62.6)		0.114
KPS							
<80	18	22.0%	23	28.0%	41	25.0%	0.471
≥80	64	78.0%	59	72.0%	123	75.0%	
Extent of resection at re-operation							
GTR	60	73.2%	59	72.0%	119	72.6%	1.000
STR	22	26.8%	23	28.0%	45	27.4%	
Recurrence interval, median (IQR)	20.8 (11.9-32.5)		9.7 (5.6-15.3)		13.2 (7.7-22.8)		<0.001
Recurrence pattern							
In-field	52	63.4%	63	76.8%	115	70.1%	0.152
Marginal	6	7.3%	5	6.1%	11	6.7%	
Out-field	24	29.3%	14	17.1%	38	23.2%	
MGMT							
Unmethylated	42	51.2%	51	62.2%	93	56.7%	0.207
Methylated	40	48.8%	31	37.8%	71	43.3%	
EGFR							
Wild type	35	42.7%	28	34.1%	63	38.4%	0.663
Mutation	30	36.6%	30	36.6%	60	36.6%	
Unknown	17	20.7%	24	29.3%	41	25.0%	
CDKN2A/B							
No homozygous deletion	12	14.6%	20	24.4%	32	19.5%	0.057
Homozygous deletion	24	29.3%	14	17.1%	38	23.2%	
Unknown	46	56.1%	48	58.5%	94	57.3%	
TERTp							
No mutation	15	18.3%	14	17.1%	29	17.7%	0.147
Mutation	20	24.4%	7	8.5%	27	16.5%	
Unknown	47	57.3%	61	74.4%	108	65.9%	
TP53							
No mutation	22	26.8%	13	15.9%	35	21.3%	0.290
Mutation	14	17.1%	16	19.5%	30	18.3%	
Unknown	46	56.1%	53	64.6%	99	60.4%	
Ki-67, median (IQR)	25.0 (14.2-45.0)		25.0 (15.0-36.0)		25.0 (15.0-41.6)		0.541
Post-operative systemic chemotherapy							
No	41	50.0%	29	35.4%	70	42.7%	0.082
Yes	41	50.0%	53	64.6%	94	57.3%	

CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; EGFR, epidermal growth factor receptor; GTR, gross total resection; IQR, interquartile range; KPS, Karnofsky performance status; MGMT, O-6-methylguanine-DNA methyltransferase; re-RT, re-irradiation; STR, subtotal resection; TERTp, telomerase reverse transcriptase promoter; TP53, tumor protein p53.

interval, *TERT* promoter mutation, *CDKN2A/B* homozygous deletion, and KPS.

The results of the risk-group-adapted approach based on the four most favorable factors (recurrence interval, *TERT* promoter mutation, *CDKN2A/B* homozygous deletion, and KPS) for post-operative re-RT are presented in Figure 1B-C. For patients with a limited number of re-RT-favoring factors (0-1 factors), post-operative re-RT did not provide a survival

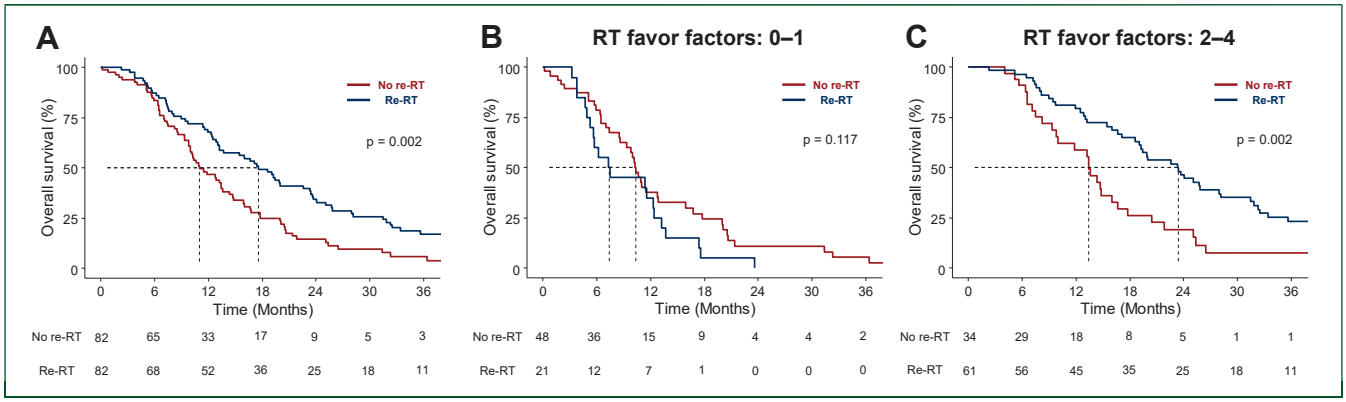

Figure 1. Overall survival following re-operation according to post-operative re-irradiation (re-RT). (A) Overall survival following re-operation based on whether patients received post-operative re-irradiation (re-RT). (B) Overall survival following re-operation for patients with a small number of radiotherapy (RT)-favoring factors (0-1 factors). (C) Overall survival following re-operation for patients with a large number of RT-favoring factors (2-4 factors).

Table 2. Cox proportional hazards regression analysis for overall survival

Variable	Univariable		Multivariable	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age				
<60	1 [Ref]	[Ref]	NA	NA
≥60	1.10 (0.78-1.57)	0.585	NA	NA
Sex				
Male	1 [Ref]	[Ref]	NA	NA
Female	0.74 (0.53-1.04)	0.087	NA	NA
KPS				
<80	1 [Ref]	[Ref]	1 [Ref]	[Ref]
≥80	0.66 (0.45-0.98)	0.040	0.24 (0.08-0.69)	0.008
Resection extent				
GTR	1 [Ref]	[Ref]	1 [Ref]	[Ref]
Non-GTR	1.54 (1.05-2.25)	0.026	3.35 (0.96-11.77)	0.059
Recurrence interval				
<12	1 [Ref]	[Ref]	NA	NA
≥12	0.38 (0.27-0.54)	<0.001	NA	NA
Recurrence pattern				
In-field/marginal	1 [Ref]	[Ref]	1 [Ref]	[Ref]
Out-field	1.66 (1.12-2.45)	0.011	4.72 (1.81-12.29)	0.002
MGMT				
Unmethylated	1 [Ref]	[Ref]	NA	NA
Methylated	0.92 (0.65-1.32)	0.662	NA	NA
EGFR				
Wild type	1 [Ref]	[Ref]	1 [Ref]	[Ref]
Mutation	1.57 (1.08-2.29)	0.019	2.46 (0.88-6.86)	0.086
CDKN2A/B				
No homozygous deletion	1 [Ref]	[Ref]	1 [Ref]	[Ref]
Homozygous deletion	1.09 (0.67-1.77)	0.727	5.24 (1.48-18.56)	0.010
TERTp				
No mutation	1 [Ref]	[Ref]	NA	NA
Mutation	1.15 (0.71-1.87)	0.560	NA	NA
TP53				
No mutation	1 [Ref]	[Ref]	NA	NA
Mutation	1.17 (0.69-1.98)	0.567	NA	NA
Ki-67				
<20%	1 [Ref]	[Ref]	NA	NA
≥20%	1.30 (0.92-1.83)	0.136	NA	NA
Post-operative re-irradiation				
No	1 [Ref]	[Ref]	1 [Ref]	[Ref]
Yes	0.58 (0.41-0.82)	0.002	0.16 (0.04-0.65)	0.011
Post-operative systemic therapy				
No	1 [Ref]	[Ref]	1 [Ref]	[Ref]
Yes	0.75 (0.54-1.06)	0.104	0.35 (0.14-0.89)	0.028

CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; CI, confidence interval; EGFR, epidermal growth factor receptor; GTR, gross total resection; HR, hazard ratio; KPS, Karnofsky performance status; MGMT, O-6-methylguanine-DNA methyltransferase; TERTp, telomerase reverse transcriptase promoter; TP53, tumor protein p53.

benefit (median OS 7.4 versus 10.3 months, $P = 0.117$) (Figure 1B). Conversely, for those with a larger number of re-RT-favoring factors (2-4 factors), post-operative re-RT demonstrated a significant survival benefit (median OS 23.4 versus 13.4 months, $P = 0.002$) (Figure 1C).

Toxicity

Among the 206 patients who underwent re-RT, RT necrosis occurred as follows: grade 5, one patient (0.5%); grade 4, four patients (1.9%); grade 3, two patients (1.0%); and grade 2, 16 patients (7.8%). Analysis of grade 2 or higher RT necrosis is presented in Table 3. Multivariate analysis revealed that recurrence outside the previous RT field (HR 0.35, $P = 0.033$) and prior surgical resection of the lesion before re-RT (HR 0.27, $P = 0.017$) were significantly associated with a lower risk of grade 2 or higher RT necrosis. The incidence of 3-year RT necrosis was 13% [95% confidence interval (CI) 8.1%-18.0%] among all patients, 5.8% (95% CI 1.9%-13.0%) among patients who underwent surgery, and 5.9% (95% CI 1.5%-15.0%) among those who achieved GTR.

DISCUSSION

Therapeutic strategies for rGBM are less standardized than initial treatments, with various options considered based on the patient's condition, tumor location, and recurrence patterns. These include re-OP, re-RT, systemic therapy, clinical trials, and the best supportive care.[7,23,24] Studies have suggested that when feasible, re-OP significantly improves rGBM outcomes. Furthermore, re-RT has proven to be a viable option.[25] A secondary analysis of the RTOG 0525 trial indicated that re-RT enhanced OS compared with best supportive care alone, particularly when combined with systemic therapy.[16] A comprehensive meta-analysis supported

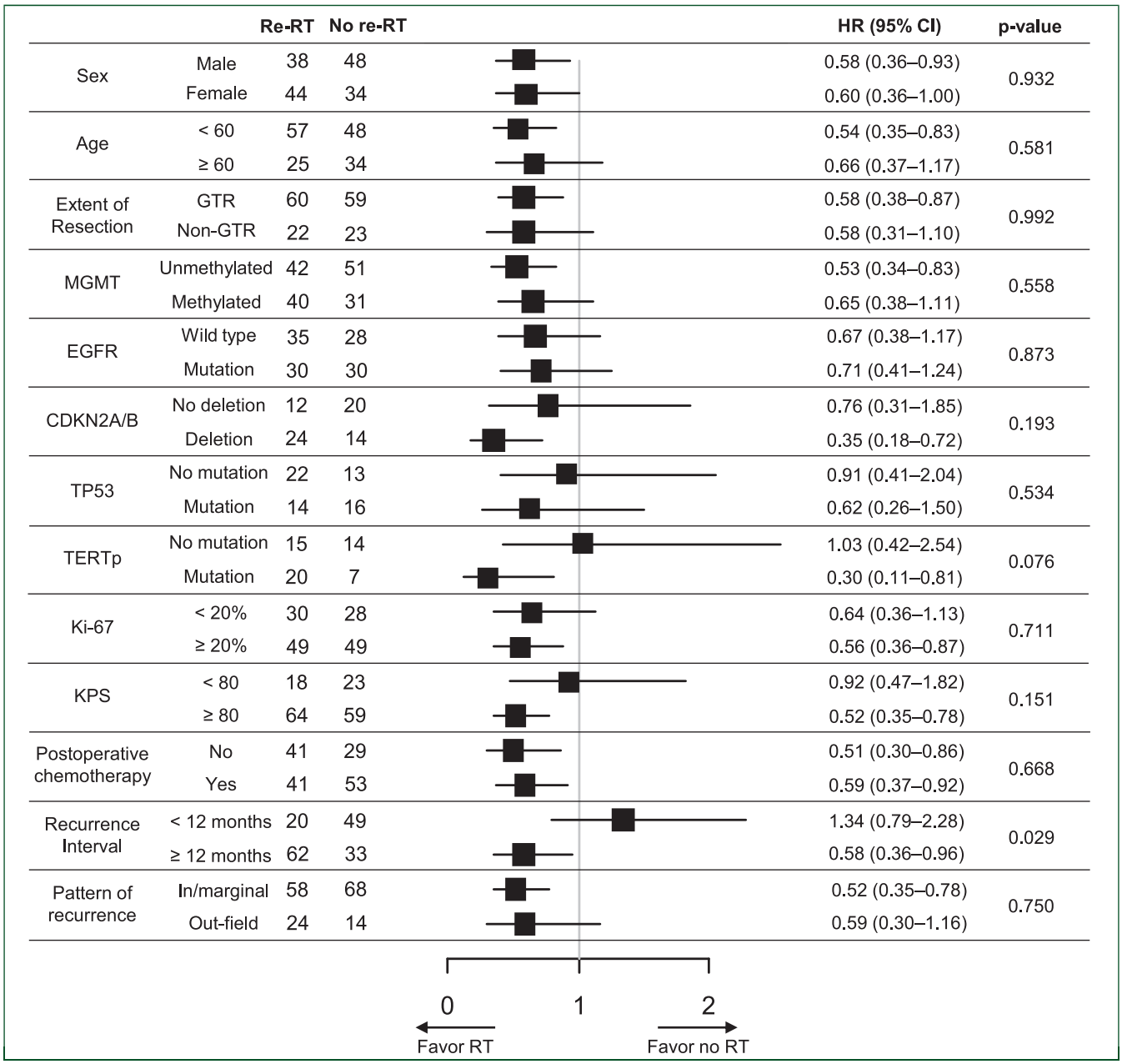

Figure 2. Forest plot of subgroup analysis evaluating factors influencing the efficacy of post-operative re-irradiation.
CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; CI, confidence interval; EGFR, epidermal growth factor receptor; GTR, gross total resection; HR, hazard ratio; KPS, Karnofsky performance status; MGMT, O-6-methylguanine-DNA methyltransferase; re-RT, re-irradiation; STR, subtotal resection; TERTp, telomerase reverse transcriptase promoter; TP53, tumor protein p53

the role of re-RT in improving disease control and prolonging survival.[17] Recent data from the multicenter KROG 21-02 study showed that combined therapeutic approaches, including re-OP, re-RT, and/or chemotherapy, improved survival outcomes compared with other treatment options.[18] The most recent study NRG Oncology/RTOG 1205 further demonstrated that re-RT combined with bevacizumab significantly improved the 6-month PFS rate compared with bevacizumab alone, although it did not extend OS, reinforcing the potential of re-RT as a valuable treatment option for rGBM.[14] Additionally, other recent studies have highlighted the efficacy of re-RT combined with bevacizumab in improving survival outcomes for patients with recurrent GBM, particularly those resistant to bevacizumab monotherapy.[26,27] However, the advantages of re-RT in the post-operative setting after re-OP remain unclear. An Italian multicenter study confirmed that re-RT for gliomas, including GBM, is safe and feasible, with 19% of participants having undergone surgery previously.[28] A smaller, single-center study involving 25 patients suggested that performing re-RT after maximal resection could prolong survival,[13] whereas a pooled analysis of 44 patients from two centers indicated no added benefit.[29] These conflicting findings arise from the limited scope of single-center studies and small sample sizes, highlighting the need for comprehensive evidence. Nevertheless, the findings highlight the

Table 3. Competing risk regression analysis for grade 2 or severe radiation necrosis

Variable	Univariable		Multivariable	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age				
<60	1 [Ref]	[Ref]	NA	NA
≥60	1.17 (0.50-2.73)	0.712	NA	NA
Sex				
Male	1 [Ref]	[Ref]	NA	NA
Female	0.87 (0.38-2.00)	0.743	NA	NA
Recurrence interval				
<12	1 [Ref]	[Ref]	NA	NA
≥12	0.84 (0.37-1.94)	0.686	NA	NA
Recurrence pattern				
In-field/marginal	1 [Ref]	[Ref]	1 [Ref]	[Ref]
Out-field	0.38 (0.14-1.02)	0.054	0.35 (0.14-0.92)	0.033
Re-OP before re-RT				
No	1 [Ref]	[Ref]	1 [Ref]	[Ref]
Yes	0.31 (0.10-0.91)	0.033	0.27 (0.09-0.79)	0.017
Cumulative radiation dose (EQD2, $\alpha/\beta = 2$)				
<110 Gy	1 [Ref]	[Ref]	NA	NA
≥110 Gy	1.15 (0.36-3.70)	0.813	NA	NA
Post-operative systemic therapy				
No	1 [Ref]	[Ref]	1 [Ref]	[Ref]
Yes	3.02 (1.11-8.23)	0.031	2.54 (0.92-6.98)	0.072

CI, confidence interval; EQD2, equivalent dose in 2 Gy fractions; HR, hazard ratio; re-OP, re-operation; re-RT, re-irradiation.

need for more comprehensive evidence. Furthermore, previous studies have not adequately considered genetic biomarkers. Building on the KROG 21-02 findings, which demonstrated survival benefits from surgical resection combined with radio(chemo)therapy, this large multicenter cohort study aimed to clarify the specific benefits of post-operative re-RT in patients with rGBM. By conducting a comprehensive analysis and incorporating genetic biomarkers, we aimed to identify specific subgroups of patients who would benefit the most from post-operative RT. This approach aimed to provide a novel decision-making strategy for managing rGBM and optimizing treatment outcomes based on individual patient characteristics.

Although the previous KROG 21-02 study suggested benefits from combining surgery and re-RT, it did not specifically analyze which post-operative patients could benefit from re-RT. Our findings, which included data from more institutions and a larger patient cohort than the previous study, revealed that post-operative re-RT, along with well-established prognostic factors such as performance status and recurrence pattern, significantly influenced overall prognosis. However, contrary to prior studies indicating a dose-response relationship at higher doses,[25] our study did not find this association to be significant. This discrepancy may arise from the lack of a clear dose-response relationship when re-RT is administered post-operatively, unlike in nonsurgical settings. Additionally, most patients receiving high-dose re-RT exhibit out-of-field recurrence, which is generally associated with poor prognosis. Although high doses could be administered in these cases, the inherently poor prognosis of out-field recurrence likely diminished the overall therapeutic benefit, as evidenced by significantly higher doses administered to these patients compared with those with in-field or marginal recurrence (mean re-RT equivalent dose in 2-Gy fractions, $\alpha/\beta = 8$, 51.4 versus 47.1; $P = 0.021$). Consequently, our study did not determine the optimal re-RT dose.

Homozygous deletions of *CDKN2A/B* and *TERT* promoter mutations are well-established negative prognostic factors for survival. *CDKN2A/B*, also known as *p16INK4A* or *p14ARF*, encodes proteins crucial for cell cycle regulation and tumor suppression.[30,31] The relationship between homozygous *CDKN2A/B* deletion and the effectiveness of re-RT in patients with rGBM remains unclear because *CDKN2A/B* plays a role in cell cycle arrest and DNA repair after irradiation; its loss may increase the susceptibility of tumor cells to RT, despite its association with poor outcomes.[32-34] Similarly, *TERT* promoter mutations, which are among the most common genetic alterations in GBMs, promote uncontrolled cancer cell proliferation and typically lead to poor outcomes.[32,35,36] However, subgroup analysis in our study revealed that post-operative re-RT provided a greater benefit to patients with these genetic alterations. The findings suggest that a more aggressive treatment strategy may be advantageous for patients who are expected to have poorer outcomes.[37-39]

Necrosis is a significant concern after re-RT. The previous KROG 21-02 study reported the incidence of toxicity but did not address predictive factors for necrosis. In the current study, the analysis of 206 patients who underwent re-RT revealed an overall 3-year incidence of RT necrosis of 13%, indicating a relatively low risk. Predictive factors included recurrence patterns and whether re-OP was carried out before re-RT. The risk was higher when recurrence occurred within a previously irradiated field but decreased following re-OP, highlighting the safety of re-RT in the post-operative setting. The 3-year incidence of RT necrosis was reduced by more than half in patients who underwent surgery, thus

dropping to 5.8%. This demonstrates that re-RT after surgery carries a relatively low risk of necrosis and can be safely administered. The low incidence and safety of RT-induced necrosis in our study can be attributed to the use of a cumulative equivalent dose in 2-Gy fractions of 100-120 Gy, which is considered safe in the majority of patients.

This study had several limitations. First, its retrospective design may have introduced significant variability between the cohorts. Moreover, re-operation was offered primarily to patients with localized, potentially resectable recurrences, which may have introduced selection bias. Although multivariate analyses were employed to mitigate this issue, caution is warranted when interpreting the results. Second, access to biomarker data was restricted. Despite the larger scale of our study compared with previous studies involving patients with rGBM, only a subset of patients had biomarker data available. This limitation necessitated the exclusion of many patients from the multivariable and subgroup analyses, thereby weakening the statistical significance. Third, the evaluation parameters used in this study were limited. Notably, the planning target volume, which has been reported as a significant factor in previous studies,[40-42] was not considered. Finally, although we assessed performance status at the time of rGBM diagnosis and recorded re-RT—related toxicity, specifically RT necrosis, other post-operative complications, and RT-associated adverse events were not systematically evaluated. The diagnosis of RT necrosis was based on clinical and radiographic findings, reflecting real-world practice; however, this approach lacks the diagnostic certainty of histopathological confirmation.

Conclusion

The current study suggests that post-operative re-RT might improve OS in a homogeneous group of patients with rGBM, following standard temozolomide-based chemoradiation with low toxicity. Our findings align with those of a previously reported KROG 21-02 study, highlighting the potential benefits of the combined treatment approach even in a post-operative context. Moreover, our research indicates that a specific subgroup of patients characterized by genetic biomarkers and clinical factors could benefit more from re-RT. These findings emphasize the need for further research to confirm the results and refine the criteria for identifying patients most likely to benefit from re-RT.

DATA AVAILABILITY

The data will be accessible from the corresponding author upon reasonable request following publication.

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DISCLOSURE

The authors have declared no conflicts of interest.

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