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Reduced volume intensity-modulated radiotherapy with simultaneous integrated boost for patients with high-grade glioma

A retrospective observational study

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Abstract

Radiotherapy (RT) is an essential treatment for patients with high-grade gliomas. however, a consensus on the target area of RT has not yet been achieved. In this study, we aimed to analyze progression-free survival (PFS), recurrence patterns, and toxicity in patients who received reduced volume intensity-modulated radiotherapy with simultaneous integrated boost (rvSIB-IMRT). In addition, we attempted to identify prognostic factors for recurrence. Twenty patients with high-grade gliomas who received rvSIB-IMRT between July 2011 and December 2021 were retrospectively analyzed. For rvSIB-IMRT, clinical target volume 1/2 was set at a 5 to 10 mm margin on each gross tumor volume (GTV) 1 (resection cavity and enhanced lesion) and GTV2 (high-signal lesion of T2/fluid-attenuated inversion recovery). RT doses were prescribed to 60 Gy/30 fractions (fxs) for planning target volume (PTV)1 and 51 to 54 Gy/30 fxs for PTV2. The median PFS and overall survival of the total cohorts were 10.6 and 13.6 months, respectively. Among the 12 relapsed patients, central, in-field, and marginal recurrences were identified in 8 (66.7%), 2 (16.7%), and 1 patient (8.3%), respectively. Distant recurrence was identified in 3 patients. Gross total resection (GTR) and high Ki-67 index (>27.4%), and subventricular involvement (SVI) were identified as significant factors for PFS in the multivariate analysis. During the follow up, 4 patients showed pseudoprogression and 1 patient showed radiation necrosis. The rvSIB-IMRT for high-grade gliomas resulted in comparable PFS and tolerable toxicity. Most recurrences were central/in-field (10 cases of 12, 83.4%). GTR, high Ki-67 index (>27.4%), and SVI were significant factors for recurrence.

Abbreviations: fxs = fractions, GTR = gross total resection, GTV = gross tumor volume, MGMT = DNA repair enzyme O (6)-methylguanine-DNA methyltransferase, MRI = magnetic resonance imaging, OS = overall survival, PFS = progression-free survival, PTV = planning target volume, RT = radiotherapy, rvSIB-IMRT = reduced volume intensity-modulated radiotherapy with simultaneous integrated boost, SVI = subventricular involvement, WHO = World Health Organization.

Keywords: high-grade glioma, prognostic factor, radiotherapy, recurrence pattern, simultaneous integrated boost

1. Introduction

High-grade gliomas account for more than half of all primary central nervous system tumors.[1] Trimodality therapy, which combines maximal safe resection, followed by adjuvant radiotherapy (RT) and concurrent or adjuvant chemotherapy, is the standard treatment. Nevertheless, high-grade glioma shows a high recurrence rate and poor prognosis, with a median survival of 13.4 to 26 months.[2,3] Age, performance status, extent of resection, and methylation of the promoter of the DNA repair enzyme O (6)-methylguanine-DNA methyltransferase (MGMT) are known as a significant prognostic factor for survival.[4–6] To reduce the high recurrence rate and improve the survival of patients with glioblastoma, adjuvant RT dose escalation studies have been conducted; however, a survival benefit has not been demonstrated,[7–11] and the currently most widely used RT dose is 60 Gy. There is no clear consensus on the delineation of the target volume for RT. Currently, the most widely accepted guidelines are those of the Radiation Therapy Oncology Group[12] and the European Organization for Research and Treatment of Cancer,[13] which are based on a margin of 2 cm on gross tumor volume (GTV), but differ in the inclusion of peritumoral edema. The National Comprehensive Cancer Network guidelines allow narrower margins than these 2 guidelines, up to 1 cm from the GTV in high-grade glioma. In

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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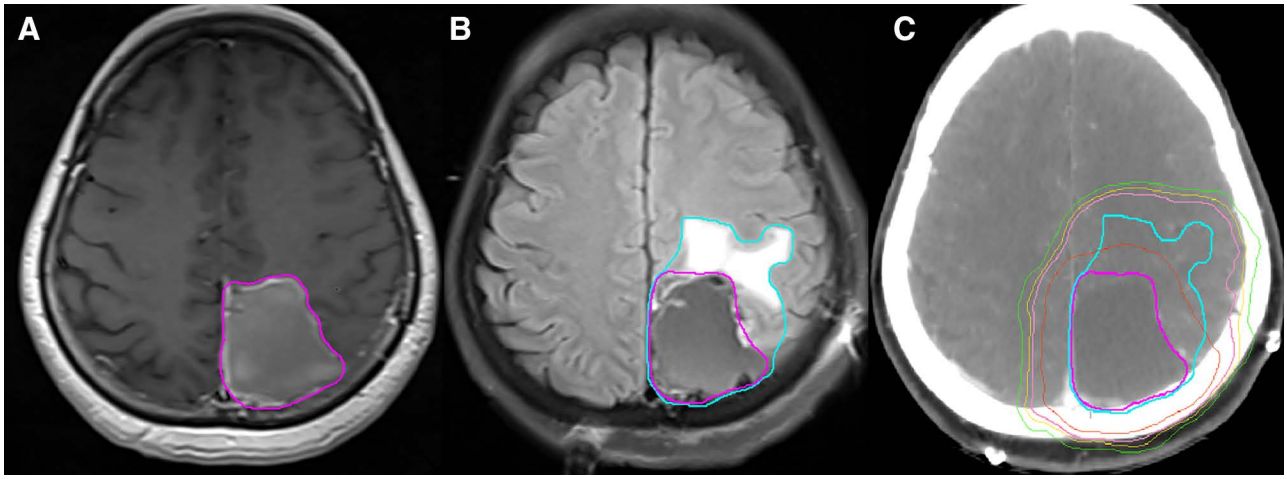

Figure 1. The plan of reduced volume intensity-modulated radiotherapy with simultaneous integrated boost in patients with glioblastoma. (A) Axial enhanced T1 weighted image (B) Axial fluid-attenuated inversion recovery (FLAIR) image (C) RT planning of patients with glioblastoma. Enhanced lesion and resection cavity of enhanced T1 weighted images was contoured as GTV1 (magenda line). High-signal area (peritumoral edema) of T2/FLAIR of magnetic resonance imaging was contoured as GTV2 (cyan line). CTV1/2 were set with 1 cm and 5 mm margins on GTV1 and GTV2, respectively. RT dose was prescribed 60 Gy for PTV1 and 54 Gy for PTV2 (red line-60 Gy isodose curve, pink line-54 Gy isodose curve, yellow line-51 Gy isodose curve, green line-46 Gy isodose curve).

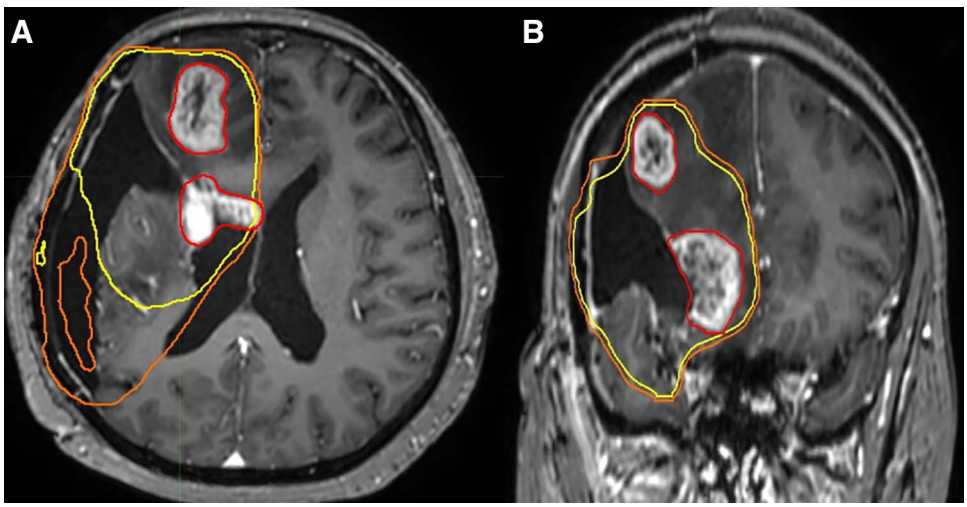

Figure 2. The analysis of recurrence pattern. (A) Axial enhanced T1 weighted image (B) Coronal enhanced T1 weighted image. Axial enhanced T1-weighted image at the first recurrence was fused with computed tomography of radiotherapy planning. All the recurrent masses were contoured by 1 radiation oncologist. The volumes of recurrent mass (red line) within 95% isodose line (57 Gy, yellow line) and 90% isodose line (54 Gy, orange line) of prescription dose (60 Gy) were analyzed. The patient showed central recurrence (more than 95% of recurrence volume was in 95% isodose line [IDL] of prescription dose [60 Gy]).

this study, we retrospectively analyzed the clinical outcomes, recurrence patterns, and toxicity of reduced volume-intensity-modulated radiotherapy with simultaneous integrated boost (rvSIB-IMRT) using a narrower margin of 5 to 10 mm. In addition, we attempted to identify the prognostic factors for recurrence in rvSIB-IMRT.

2. Methods

2.1. Patients

The retrospective analysis was performed for 20 patients who received rvSIB-IMRT among 50 patients who underwent RT with histologically confirmed World Health Organization (WHO) grade 3 of glioma or glioblastoma from February 2011 to December 2021. The inclusion criteria were: age ≥ 18 yeas, surgically resected or pathologically confirmed WHO grade 3 glioma or glioblastoma, patients who completed the RT of definitive aim, and follow up performed after RT with periodic contrast enhanced magnetic resonance imaging (MRI). The correlation between recurrence and prognostic factors, such as age, resection extent, Ki-67 index (%), midline involvement, and subventricular involvement (SVI) was analyzed. Midline involvement was defined as a lesion abutting the falx cerebri or extending to the contralateral hemisphere on brain MRI. SVI was defined as the abutment of the enhanced lesion of a tumor to the subventricular zone or invasion of the ventricular lining in preoperative contrast-enhanced T1-weighted MRI, or when ventricular invasion is confirmed during surgery. This study was approved by the institutional review board of the Catholic Medical Center ethics committee (IRB No. OC23RASI0045).

2.2. Treatment

All patients were histologically confirmed with WHO grade 3 astrocytoma or oligodendroglioma, and glioblastoma by surgical resection or biopsy. All patients underwent treatment based on maximal safe resection and 3 patients who did not

Table 1

Clinical and treatments characteristics of patients.

Factor		N. (%) (total, N.= 20)
Age	Median, 57 years (range, 29–75 yr)	
Gender	Male	10 (50%)
	Female	10 (50%)
Pathological diagnosis	Glioblastoma	15 (75%)
	Astrocytoma, WHO grade 3	4 (20%)
	Oligodendroglioma, WHO grade 3	1 (5%)
Initial symptom	Headache	8 (40 %)
	Cognitive impairment	3 (15 %)
	Drowsy mental state	1 (5%)
	Limb weakness	4 (20%)
	Diplopia	1 (5%)
	Seizure	1 (5%)
	Tremor	1 (5%)
	Abnormal image finding	1 (5%)
KPS score	50–70	3 (15%)
	80–100	17 (85%)
Tumor maximal diameter (cm)	<4 cm	5 (25%)
	4–6 cm	11 (55%)
	>6 cm	4 (20%)
Midline involvement	Yes	7 (35%)
	No	13 (65%)
Subventricular involvement	Yes	14 (70%)
	No	6 (30%)
IDH mutation	Mutant	3 (15%)
	Wild type	17 (85%)
MGMT methylation	Yes	9 (45%)
	No	9 (45%)
	Unknown	2 (10%)
Ki-67 index	Median, 27.4% (range, 0.3%–76.4%)	
Resection	Gross total resection	10 (50%)
	Subtotal resection	7 (35%)
	Biopsy	3 (15%)
Radiotherapy dose	PTV1, 60 Gy/30 fractions	20 (100%)
	PTV2, 51 Gy/30 fractions	1 (5%)
	PTV2, 52.5 Gy/30 fractions	1 (5%)
	PTV2, 54 Gy/30 fractions	18 (90%)

fxs = fractions, IDH = isocitrate dehydrogenase, KPS = Karnofsky Performance Scale, MGMT = DNA repair enzyme O(6)-methylguanine-DNA methyltransferase, N = number, PTV = planning target volume, WHO = World Health Organization.

have the medical condition to undergo surgery underwent only a biopsy procedure. Resection extent was evaluated through postoperative MRI performed within 48 hours after surgery. Gross total resection (GTR) was defined as status of complete removal of contrast-enhancing tumor for glioblastoma, and T2/FLAIR hyperintensity lesion for grade 3 glioma in postoperative MRI. Resection of tumor was performed; however, cases that did not reach the GTR were classified as subtotal resection (STR). Biopsy was defined as a case performed for pathological diagnosis without a reduction in tumor volume in postoperative MRI. Surgical extent was defined through referring to the category recommendation for extent of resection suggested by Philipp et al.[14] Patients with grade 3 gliomas received adjuvant RT, followed by 6 cycles of procarbazine, lomustine, and vincristine (PCV) chemotherapy after surgery. Patients with glioblastoma underwent postoperative concurrent chemoradiotherapy with temozolomide (75 mg/m^2/day) followed by 6 cycles of temozolomide maintenance chemotherapy (150–200 mg/m^2/day). RT was initiated within 2 to 6 weeks after surgery and was delayed in some patients up to 8 weeks after surgery because of surgical wound management or postoperative care. The mean interval between surgery and initiation of RT was 32.4 days (range 17–53 days). RT was planned with reference to enhanced brain MRI performed within 48 hours after surgery and preoperative MRI. GTV1 was contoured on the surgical cavity and enhanced lesion on contrast-enhanced T1-weighted MRI. GTV2 was contoured on high-signal areas on T2-weighted and fluid-attenuated inversion recovery images. Clinical target volume (CTV) 1 and 2 were set with a 5 to 10 mm margin from GTV1 and 2, respectively. The planning target volume (PTV)1 and 2 were set with a 0 to 3 mm margin from CTV1 and 2, respectively. An RT dose of 60 Gy/30 fractions (fxs) for PTV1 and 51 to 54 Gy/30 fxs (fxs size, 170 to 180 cGy) for PTV2 was prescribed. An example of an RT plan is shown in Figure 1.

2.3. Follow-up and evaluation of recurrence and toxicity

The patients underwent response evaluation with enhanced MRI 1 month after completion of RT, and periodic follow up was performed with brain MRI every 3 months. Progression-free survival (PFS) and overall survival (OS) were defined as the date of the first recurrence or death or the date of the last follow-up visit from the date of surgery, respectively. Progression was diagnosed when enhancing lesions increased 25% or more in the sum of the products of perpendicular diameters, or the development of new lesions according to the Neuro-Oncology Working Group response assessment in neuro-oncology criteria. To differentiate between pseudoprogression and true progression, we referred to the timing of lesion occurrence from the completion of RT, and serial MRI findings. Pseudoprogression was diagnosed when a progressive lesion developed 2 to 6 months after the completion of RT and showed a pattern of gradual remission thereafter. In addition, diffusion-weighted and perfusion MRI was used to discriminate between pseudoprogression and progression. Differential diagnoses were also discussed at a multidisciplinary meeting involving neurosurgeons, radiologists, and radiation oncologists. To analyze the recurrence pattern, enhanced brain MRI at the occurrence of the first recurrence and computed tomography (CT) of RT planning were fused using the MIM software version 7.0.8 (MIM software Inc. Cleveland, OH). All recurrent masses were contoured by 1 radiation oncologist and compared to the isodose line of the RT plan (Fig. 2). Recurrence patterns were defined as "central recurrence" (if more than 95% of recurrence volume was in 95% isodose line (IDL) of 60 Gy), "in-field recurrence" (if more than 95% of recurrence volume was in high dose region (90% IDL of 60 Gy), and "marginal recurrence" (<95% of recurrent volume was outside the 90% IDL of 60 Gy). Central, in-field and marginal recurrences were categorized as local recurrence. Recurrence that occurred outside the RT field (<50% IDL of 60 Gy) was defined as "distant recurrence." The radiation necrosis was diagnosed when showing typical feature like "Swiss cheese" or "Soap-bubble" that had peripheral enhancement and central hypointensity on post-contrast T1-weighted image and showing high signal in white matter in T2-weighted images.[15] When additional perfusion MRI was performed, cases in which the cerebral blood volume was reduced within the lesion were diagnosed as radiation necrosis.

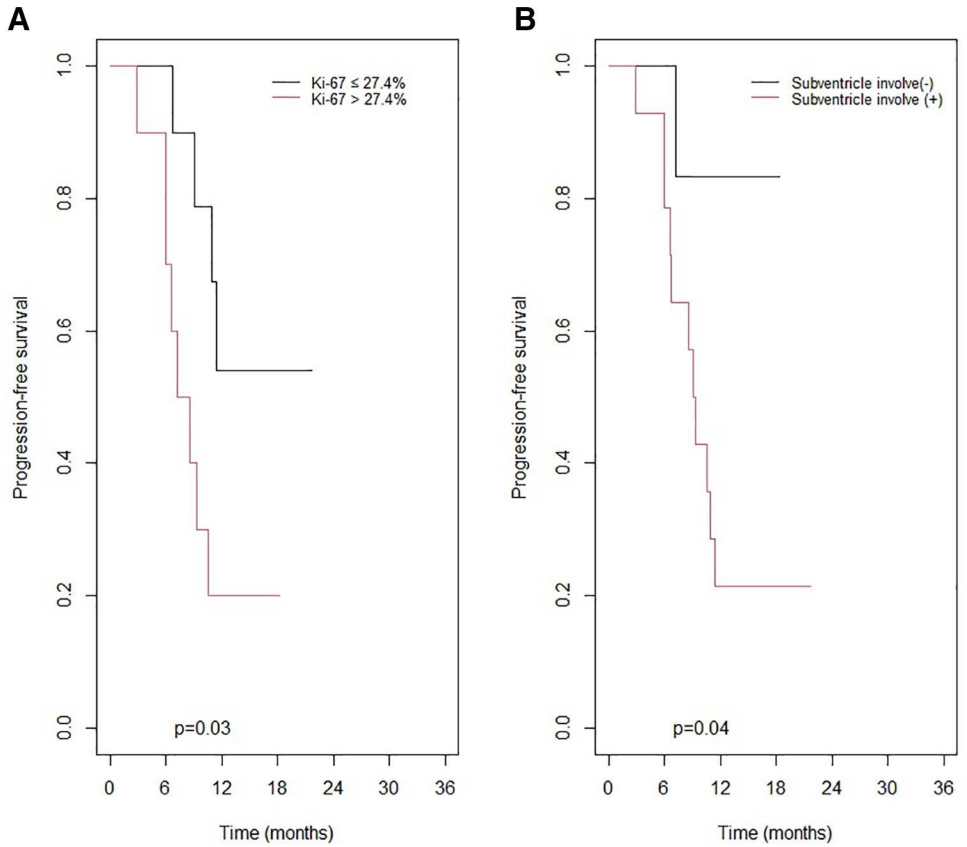

Figure 3. Kaplan–Meier survival curve for progression free survival according to prognostic factors. (A). The group of high Ki-67 index (>27.4%) showed significantly lower progression-free survival than that of low Ki-67 index (≤27.4%) (B). The group of subventricular involvement (+) showed significantly lower progression-free survival than that of subventricular involvement (–).

Table 2

Univariate analysis for progression-free survival.

Factor		N. Total, 20	6-mo PFS (%)	1-yr PFS (%)	*P* value
Age	≤60 yr	12	75	28.1	.7
	>60 yr	8	62.5	50	
Gender	Male	10	90	35	.6
	Female	10	80	40	
Initial neurologic symptom	Yes	8	100	37.5	.5
	No	12	75	40	
KPS score	≤70	3	100	66.7	.4
	>70	17	82.4	30.8	
MGMT methylation	Yes	9	88.9	22.2	.2
	No	9	77.8	48.6	
Tumor maximal diameter	<4 cm	5	100	40	.8
	≥4 cm	15	80	37	
Resection	GTR	10	90	50	.3
	STR/Biopsy	10	80	24	
Ki-67 index (%)	≤27.4	10	100	54	.03*
	>27.4	10	70	20	
Midline involvement	Yes	7	85.7	34.3	.7
	No	13	84.6	38.5	
Subventricular involvement	Yes	14	78.6	21.4	.04*
	No	6	100	83.3	

GTR = gross total resection, KPS = Karnofsky Performance Scale, MGMT = DNA repair enzyme O(6)-methylguanine-DNA methyltransferase, mo = months, N = number, PFS = progression-free survival, STR = subtotal resection, yr = years

*Statistically significant.

2.4. Statistical analysis

The patients' actuarial PFS and OS were calculated using the Kaplan–Meier method, and the log-rank test was used to analyze the significance of prognostic factors and recurrence. The Ki-67 index was classified into 2 group based on the medial value of 27.4. Multivariate analysis was conducted using the Cox proportional hazards model and included a factor with a *P* value of <.05 in the univariate analysis or considered clinically important. All statistical analyses were performed using the R program version 4.0.1 (R Development Core Team, Vienna, Austria), and a *P* value <.05 was considered statistically significant.

3. Results

3.1. Clinical characteristics of patients

The retrospective analysis was performed of 20 patients with high-grade glioma who received rvSIB-IMRT. The median follow-up duration was 12.9 months (range, 6.7 to 21.6 months). The median age of the patients was 57 years (range, 29–75 years), and the male-to-female ratio was 1:1. Histologically, the most common were glioblastomas (15 of 20 patients, 75%), and grade 3 astrocytoma and oligodendroglioma were 4 and 1, respectively. Headache (8 patients, 40%) was the most common initial symptom, followed by limb weakness (4 patients, 20%) and cognitive impairment (3 patients, 15%). Three patients showed a poor performance status, with a KPS score of <70. GTR and STR were performed in 10 (50%) and 7 patients, respectively. The other 3 patients underwent biopsy only. Three patients (15%) showed the IDH-mutant type and 9

patients (45%) showed methylation of the MGMT promoter. In 2 patients, status of MGMT methylation was unknown. Seven patients (35%) showed midline involvement on MRI, and 14 patients (70%) showed SVI on preoperative diagnostic MRI or surgical findings. The median Ki-67 index was 27.4% (range, 0.3%–76.4%). Details of the patients' clinical and treatments characteristics are shown in Table 1.

3.2. Survival and recurrence pattern

Fourteen patients (70%) died, and recurrence occurred in 12 patients (of 20 patients, 60%) at the time of analysis. The median PFS and OS were 10.6 and 13.6 months, respectively. Among the 12 relapsed patients, 9 had local recurrence, 1 had distant recurrence, and 2 experienced simultaneous local and distant brain sites. Of the 3 distant recurrences, 2 were confirmed in the contralateral hemisphere and one was confirmed in the fourth ventricle through cerebrospinal fluid seeding. Central, in-field, and marginal recurrences were identified in 8 (66.7%), 2 (16.7%), and 1 (8.3%) of the total 12 relapsed patients, respectively.

3.3. Prognostic factors for recurrence

In the univariate analysis of PFS, the group with a high Ki-67 index (>27.4%) showed a significantly lower 1-year PFS than the low Ki-67 index group (≤27.4%) (20% vs 54%, $P = .03$) (Fig. 3). The SVI was identified negative prognostic factor for 1-year PFS (SVI (+) versus SVI (–); 21.4% versus 83.3%, $P = .04$) (Fig. 3). Age, KPS score, MGMT methylation, and maximum diameter of tumor were not showed significant results for PFS. Details of the univariate analysis are presented in Table 2. In the multivariate analysis, STR or biopsy was a negative prognostic factor for PFS compared with GTR (hazard ratio [HR], 1.97; 95% confidence interval [CI], 1.12–44.46; $P = .034$). In addition, the high Ki-67 index (>27.4%) (HR, 2.48; 95% CI, 1.79–79.84; $P = .011$), and SVI (HR, 2.67; 95% CI, 1.16–180.40; $P = .038$) were significant risk factor for recurrence. The results of the multivariate analysis are presented in Table 3.

Table 3

Multivariate analysis for progression-free survival.

Factor		PFS	
		HR (95% CI)	*P* value
Resection	Gross total resection Subtotal resection/Biopsy	1.97 (1.12–44.46)	.034*
Ki-67 index (%)	≤27.4 >27.4	2.48 (1.79–79.84)	.011*
Subventricular involvement	No Yes	2.67 (1.16–180.40)	.038*

CI = confidence interval, HR = hazard ratio, PFS = progression-free survival.
*Statistically significant.

3.4. Toxicity

During the follow up, of the 20 patients, 4 (20%) and 1 (10%) showed pseudoprogression and radiation necrosis, respectively. After RT, 2 cases (10%) were identified in which steroids were newly prescribed or the dose was increased from the previous dose owing to the occurrence of headache or neurological symptoms without disease progression. Both patients remained stable after steroid use.

4. Discussion

This study analyzed the PFS, recurrence pattern, and prognostic factors of rvSIB-IMRT performed with a margin of 1 cm or less in patients with high-grade glioma. The PFS of the entire cohort was 10.6 months, which was consistent with findings of other studies that reported a PFS of 7.0 to 9.4 months when analyzing data from high-grade glioma treated with combined chemoradiotherapy.[3,16,17] The median OS of this cohort was 13.6 months, showing slightly lower results compared to other studies of 17.7 to 36.5 months.[3,16,17] This may be attributed to the fact that patients with glioblastoma accounted for the majority (75%). In addition, a significant number of deaths occurred due to causes other than disease progression. Among the 14 patients who died during the follow-up period, 3 died due to pneumonia and 1 died due to suicide. In the analysis of recurrence patterns, the most common recurrence pattern was central recurrence (8 of 12 patients, 66.7%), and central/in-field recurrence accounted for 83.3% of all recurrences. These results are consistent with the recurrence patterns reported in previous studies of high-grade gliomas (Table 4). In this study, distant recurrence was

Table 4

Clinical target volume and recurrence patterns of other studies.

Studies	Margin	RT dose	Central	In-field	Marginal	Distant
McDonald et al, 2009[18]	CTV_initial, 7 mm from GTV2* CTV_boost, 5 mm from GTV1†	PTV_initial, 46 Gy/23 fxs PTV_boost, 60 Gy/30 fxs	78%	15%	5%	2%
Minniti et al, 2010[19]	CTV, 2 cm from GTV1	60 Gy/30 fxs	75.2%	5.7%	5.7%	13.3%
Zheng et al, 2021[16]	CTV1, 1 cm from GTV1 CTV2, 2 cm from GTV1	PTV1, 60 Gy/30 fxs PTV2, 54 Gy/30 fxs	80%	3.6%	1.8%	25.5%
Liu et al, 2023[17]	Plan1; CTV1, 2 cm from GTV2 Plan2; CTV2, 2 cm from GTV1	60 Gy/30 fxs	68.2%	10.6%	0%	21.2%
Our study	CTV1, 5–10 mm from GTV1 CTV2, 5–10 mm from GTV2	PTV1, 60 Gy/30 fxs PTV2, 51–54 Gy/30 fxs	66.7%	16.7%	8.3%	25%

CTV = clinical target volume, fxs = fractions, GTV = gross tumor volume, PTV = planning target volume.
*GTV2 defined as high-signal lesion (peritumoral edema) in T2-weighted and fluid-attenuated inversion recovery (FLAIR) images of brain MRI.
†GTV1 defined as postoperative enhancing tumor and resection cavity in enhanced T1-weighted brain MRI.

confirmed in 3 patients (of 12 patients [25%]), which is consistent with results of the 2% to 25.5% incidence of previous studies (Table 4). To identify risk factors related to distant recurrence, univariate analysis was performed on factors, such as MGMT methylation, midline involvement, SVI, and Ki-67 index. Although statistical significance was not shown due to the limited number of patients and events, SVI showed negative trends for 1-year distant recurrence-free survival (SVI (+) vs SVI (–), 65.2% and 100%; $P = .2$) in this study. This is consistent with the results of a study by Liu et al that identified subventricular zone involvement as a risk factor for non-local recurrence in patients with adult-type diffuse glioma who underwent temozolomide-based chemoradiotherapy.[17] A study conducted by Minniti et al suggested that the pattern of recurrence in patients with glioblastoma varied depending on the status of MGMT methylation, and that distant recurrence increased in patients with MGMT methylation (central/in-field recurrence and outside recurrence, 64% and 31%).[19] In this study, 9 patients (45%) showed MGMT methylation, and the MGMT status was unknown in 2 patients. MGMG methylation status may have contributed to the increase in distant recurrence in this study. In the analysis of local recurrence, central recurrence was the most common, and 1 case of marginal recurrence was identified. Several previous studies have analyzed recurrence patterns according to CTV margins in patients with high-grade gliomas and glioblastomas (Table 4). McDonald et al suggested that margins within 1 cm do not increase marginal or distant recurrence.[18] Paulsson et al compared and analyzed the recurrence patterns of RT using 5 mm, 10 mm, 15 to 20 mm margins and reported that recurrence patterns did not change according to the margin in patients with glioblastoma.[20] Some studies have reported that the pattern of recurrence and clinical outcome of RT, which was performed without intentionally including peritumoral edema, was similar to that of RT that included edema.[16,17] In this study, we performed rvSIB-IMRT with a narrower margin from GTV1 (resection cavity and enhancing tumor) and GTV2 (peritumoral edema) using the SIB technique without additional boost planning and showed favorable PFS without an increase in marginal and distant recurrences. In addition, we tried to identify prognostic factors for recurrence in rvSIB-IMRT, and GTR, high Ki-67 index (>27.4%), and SVI were significant factors for PFS. The favorable effect of GTR on survival has been widely known in several previous studies.[21,22] The Ki-67 index is an important indicator of tumor cell proliferation in patients of glioma.[23] High Ki-67 index has been identified as a risk factor that can decrease OS and PFS in previous studies, and various cutoff points (range, 20%–30%) have been suggested.[24–27] In a study conducted by Caramanti et al, Ki-67 index was identified as an indicator of tumor aggressiveness, which correlated with the volume of peritumoral edema.[28] In this study, we confirmed that a high Ki-67 index (>27.4%) is a risk factor for recurrence in patients with high-grade gliomas who underwent rvSIB-IMRT. Further research is needed to determine whether an increase in the margin or dose of RT can improve therapeutic outcomes in these patients who has risk factors treated with rvSIB-IMRT. In this study, SVI was found to be a negative prognostic factor for PFS. This is consistent with previous studies suggesting that high-grade gliomas adjacent to subventricular zone can decrease OS and PFS and increase distant relapse.[17,29,30] In terms of toxicity, rvSIB-IMRT exhibited acceptable toxicity. Pseudoprogression was confirmed in 4 patients (20%) and radiation necrosis in 1 patient (5%), which is similar to 14% to 23% reported in other studies of glioma.[15,31–33] This study had several limitations. As this study was a retrospective study with a small number of patients from a single institution, the number of events was limited, and the statistical analysis might be limited. However, this study suggested the feasibility and effectiveness of rvSIB-IMRT, and as identifying the risk factors, such as the SVI and high Ki-67 index, it suggested that closer follow-up or intensified therapy may be needed in these patients. These results need to be confirmed in further studies involving more patients.

In conclusion, rvSIB-IMRT resulted in comparable PFS and tolerable toxicity in patients with high-grade gliomas. Most recurrences were central/in-field (10 cases, 83.4%), and 1 marginal recurrence (8.3%) occurred. GTR, high Ki-67 index (>27.4%), and SVI were significant factors for PFS. These results need to be confirmed in further studies involving a larger number of patients.

Author contributions

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References

[1] Miller KD, Ostrom QT, Kruchko C, et al. Brain and other central nervous system tumor statistics, 2021. CA Cancer J Clin. 2021;71:381–406.
[2] Cho KH, Kim J-Y, Lee SH, et al. Simultaneous integrated boost intensity-modulated radiotherapy in patients with high-grade gliomas. Int J Radiat Oncol Biol Phys. 2010;78:390–7.
[3] Choi JW, Lee MM, Kim IA, et al. The outcomes of concomitant chemoradiotherapy followed by adjuvant chemotherapy with temozolomide for newly diagnosed high grade gliomas: the preliminary results of single center prospective study. J Korean NeurosurgSoc. 2008;44:222–7.
[4] Gittleman H, Lim D, Kattan MW, et al. An independently validated nomogram for individualized estimation of survival among patients with newly diagnosed glioblastoma: NRG Oncology RTOG 0525 and 0825. Neuro-oncology. 2017;19:669–77.
[5] Helseth R, Helseth E, Johannesen TB, et al. Overall survival, prognostic factors, and repeated surgery in a consecutive series of 516 patients with glioblastoma multiforme. Acta Neurol Scand. 2010;122:159–67.
[6] Li H, He Y, Huang L, et al. The nomogram model predicting overall survival and guiding clinical decision in patients with glioblastoma based on the SEER Database. Front Oncol. 2020;10:1051.
[7] Watkins JM, Marshall DT, Patel S, et al. High-dose radiotherapy to 78 Gy with or without temozolomide for high grade gliomas. J Neurooncol. 2009;93:343–8.
[8] Shapiro WR, Green SB, Burger PC, et al. Randomized trial of three chemotherapy regimens and two radiotherapy regimens and two radiotherapy regimens in postoperative treatment of malignant glioma. brain tumor cooperative group trial 8001. J Neurosurg. 1989;71:1–9.
[9] Chang CH, Horton J, Schoenfeld D, et al. Comparison of postoperative radiotherapy and combined postoperative radiotherapy and chemotherapy in the multidisciplinary management of malignant gliomas. A joint radiation therapy oncology group and Eastern Cooperative Oncology Group study. Cancer. 1983;52:997–1007.
[10] Ali AN, Zhang P, Yung WKA, et al. NRG oncology RTOG 9006: a phase III randomized trial of hyperfractionated radiotherapy (RT) and BCNU versus standard RT and BCNU for malignant glioma patients. J Neurooncol. 2018;137:39–47.
[11] Prados MD, Wara WM, Sneed PK, et al. Phase III trial of accelerated hyperfractionation with or without difluromethylornithine (DFMO) versus standard fractionated radiotherapy with or without DFMO for newly diagnosed patients with glioblastoma multiforme. Int J Radiat Oncol Biol Phys. 2001;49:71–7.
[12] Cabrera AR, Kirkpatrick JP, Fiveash JB, et al. Radiation therapy for glioblastoma: executive summary of an american society for radiation oncology evidence-based clinical practice guideline. Pract Radiat Oncol. 2016;6:217–25.

[13] Niyazi M, Brada M, Chalmers AJ, et al. ESTRO-ACROP guideline "target delineation of glioblastomas". Radiother Oncol. 2016;118:35–42.
[14] Karschnia P, Vogelbaum MA, van den Bent M, et al. Evidence-based recommendations on categories for extent of resection in diffuse glioma. Eur J Cancer (Oxford, Engl: 1990). 2021;149:23–33.
[15] Kumar AJ, Leeds NE, Fuller GN, et al. Malignant gliomas: MR imaging spectrum of radiation therapy- and chemotherapy-induced necrosis of the brain after treatment. Radiology. 2000;217:377–84.
[16] Zheng L, Zhou ZR, Yu Q, et al. The definition and delineation of the target area of radiotherapy based on the recurrence pattern of glioblastoma after temozolomide chemoradiotherapy. Front Oncol. 2020;10:615368.
[17] Liu H, Zhang L, Tan Y, et al. Observation of the delineation of the target volume of radiotherapy in adult-type diffuse gliomas after temozolomide-based chemoradiotherapy: analysis of recurrence patterns and predictive factors. Radiat Oncol (Lond, Engl). 2023;18:16.
[18] McDonald MW, Shu HK, Curran WJ, Jr., et al. Pattern of failure after limited margin radiotherapy and temozolomide for glioblastoma. Int J Radiat Oncol Biol Phys. 2011;79:130–6.
[19] Minniti G, Amelio D, Amichetti M, et al. Patterns of failure and comparison of different target volume delineations in patients with glioblastoma treated with conformal radiotherapy plus concomitant and adjuvant temozolomide. Radiother Oncol. 2010;97:377–81.
[20] Paulsson AK, McMullen KP, Peiffer AM, et al. Limited margins using modern radiotherapy techniques does not increase marginal failure rate of glioblastoma. Am J Clin Oncol. 2014;37:177–81.
[21] Noorbakhsh A, Tang JA, Marcus LP, et al. Gross-total resection outcomes in an elderly population with glioblastoma: a SEER-based analysis. J Neurosurg. 2014;120:31–9.
[22] Kawaguchi T, Sonoda Y, Shibahara I, et al. Impact of gross total resection in patients with WHO grade III glioma harboring the IDH 1/2 mutation without the 1p/19q co-deletion. J Neurooncol. 2016;129:505–14.
[23] Du N, Shu W, Li K, et al. An initial study on the predictive value using multiple MRI characteristics for Ki-67 labeling index in glioma. J Transl Med. 2023;21:119.
[24] Armocida D, Frati A, Salvati M, et al. Is Ki-67 index overexpression in IDH wild type glioblastoma a predictor of shorter Progression Free survival? A clinical and molecular analytic investigation. Clin Neurol Neurosurg. 2020;198:106126.
[25] Zeng A, Hu Q, Liu Y, et al. IDH1/2 mutation status combined with Ki-67 labeling index defines distinct prognostic groups in glioma. Oncotarget. 2015;6:30232–8.
[26] Henker C, Kriesen T, Schneider B, et al. Correlation of Ki-67 Index with volumetric segmentation and its value as a prognostic marker in glioblastoma. World Neurosurge. 2019;125:e1093–103.
[27] Wong E, Nahar N, Hau E, et al. Cut-point for Ki-67 proliferation index as a prognostic marker for glioblastoma. Asia-Pac J Clin Oncol. 2019;15:5–9.
[28] Caramanti R, Aprígio RM, D`Aglio Rocha CE, et al. Is edema zone volume associated with Ki-67 index in glioblastoma patients?. Cureus. 2022;14:e24246.
[29] Comas S, Luguera E, Molero J, et al. Influence of glioblastoma contact with the subventricular zone on survival and recurrence patterns. Clin Transl Oncol. 2021;23:554–64.
[30] Jafri NF, Clarke JL, Weinberg V, et al. Relationship of glioblastoma multiforme to the subventricular zone is associated with survival. Neuro-oncology. 2013;15:91–6.
[31] Chamberlain MC, Glantz MJ, Chalmers L, et al. Early necrosis following concurrent Temodar and radiotherapy in patients with glioblastoma. J Neurooncol. 2007;82:81–3.
[32] Ruben JD, Dally M, Bailey M, et al. Cerebral radiation necrosis: incidence, outcomes, and risk factors with emphasis on radiation parameters and chemotherapy. Int J Radiat Oncol Biol Phys. 2006;65:499–508.
[33] Van Mieghem E, Wozniak A, Geussens Y, et al. Defining pseudoprogression in glioblastoma multiforme. Eur J Neurol. 2013;20:1335–41.