RESEARCH ARTICLE

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Comparing the Recurrence Patterns of Reduced-Margins vs. RTOG-Protocol in Adjuvant Chemoradiation of High-Grade Gliomas: A Multicenter, Open-Label, Randomized Controlled Trial

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Abstract

Background: Radiotherapy following maximal-safe resection is a cornerstone of treatment for high-grade gliomas (HGGs). However, the optimal clinical target volume (CTV) margin remains controversial. This study aimed to evaluate the safety, efficacy, and recurrence patterns associated with a reduced CTV margin in patients with HGGs, compared to standard RTOG-based planning. **Methods:** In this multicenter, phase III randomized clinical trial, patients aged 18–75 years with newly diagnosed WHO-grade 3 or 4 gliomas were randomly assigned to receive adjuvant radiotherapy with either a standard 2-cm clinical target volume (CTV) margin (control group) or a reduced 1-cm margin (intervention group). The primary endpoint was progression-free survival (PFS), while the secondary endpoints included overall survival (OS) and patterns of recurrence. **Results:** A total of 258 patients were enrolled, of whom 75.6% had grade 4 gliomas. After a median follow-up of 14.5 months, median PFS was 15 ± 1.25 months in the intervention group but it was 19 ± 2.71 months in the control group (hazard ratio [HR] = 1.32; 95% CI, 0.93–1.87; p = 0.121). Median OS was 22.0 ± 2.98 months in the intervention group, while it was not reached in the control group (HR = 1.52; 95% CI, 0.99–2.33; p = 0.057). Imaging progression occurred in 35% of patients in the intervention group and 32.2% in the control group (p = 0.637). In-field recurrence was the predominant pattern in both groups (84% vs. 83.8%; p = 0.829), with no significant increase in marginal or out-of-field failures associated with margin reduction. **Conclusion:** Reducing the clinical target volume (CTV) margin from 2 cm to 1 cm in the adjuvant radiotherapy of high-grade gliomas did not significantly affect progression-free survival (PFS), overall survival (OS), or recurrence patterns. These findings support the feasibility and safety of margin reduction, even in settings where three-dimensional conformal radiotherapy (3D-CRT) is the primary technique.

Keywords: high grade glioma- radiotherapy- reduced margin- target delineation

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Introduction

High-grade gliomas (HGGs), comprising WHO grade 3 and 4 gliomas, represent the most aggressive primary brain tumors, accounting for the majority of malignant gliomas. Grade 4 glioma, which was formerly known as glioblastoma multiforme (GBM), is the most common subtype, representing approximately 45–54% of glial tumors, and is associated with a particularly poor prognosis [1–3]. Median overall survival (OS) ranges from 6.8 to 14.6 months for grade 4 glioma and approximately 56 months for grade 3 glioma, with a 5-year survival rate of only 5–10% for GBM [4, 5].

As for the treatment, radiotherapy remains a cornerstone of HGG management and significantly improves survival when combined with chemotherapy. Historically, whole-brain radiotherapy was the standard approach until the BTCG 80-01 trial established the non-inferiority of partial brain irradiation [6]. Subsequent pathological studies demonstrated that a 3-cm margin around the contrast-enhancing tumor typically encompassed microscopic tumor spread [7], informing protocols such as RTOG

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0525 and 0825, which delivered a total dose of 60 Gy using margins of 2–2.5 cm [8, 9]. Since then, additional protocols, including those from EORTC, ABTC, and MD Anderson Cancer Center, have adopted varying margins and treatment approaches [10–14] [Table 1].

However, radiotherapy may result in substantial long-term toxicity, including cognitive impairment, white matter injury, and cerebral atrophy [15, 16]. Consequently, reducing radiation margins without compromising tumor control represents an important clinical objective. A summary of trials evaluating the safety and feasibility of margin reduction is presented in Table 2; these have informed recent guidelines, such as those from ESTRO/ACROP, which support smaller margins (down to 1.5 cm) in selected patients [11, 14, 17–25].

This randomized clinical trial aimed to evaluate the safety, efficacy, and recurrence patterns associated with reducing the clinical target volume (CTV) margin from 2 cm to 1 cm in the adjuvant treatment of high-grade gliomas. Despite advances in radiotherapy techniques, the optimal CTV margin remains controversial, particularly in settings with limited access to IMRT or proton therapy. To our knowledge, this is the first prospective, randomized trial comparing 1-cm versus 2-cm CTV margins in patients with HGGs treated predominantly with three-dimensional conformal radiotherapy (3D-CRT) in a resource-limited setting.

Materials and Methods

Patients and Population

This Phase III, single-blind, multicenter study was conducted at three academic centers in Iran after approval by the respective institutional ethics committees. Between February 2021 and September 2022, patients aged 18–75 years were enrolled with newly diagnosed WHO grade 3 or 4 gliomas. Exclusion criteria included prior cranial radiotherapy or surgery, a history of brain tumors, medical contraindications to chemotherapy or radiotherapy, and poor performance status (Karnofsky Performance Status < 70%). The calculated sample size was 192 patients; however, 258 patients were enrolled to account for potential dropouts and non-compliance, and to ensureadequate statistical power for subgroup analyses. Randomization was performed using a computer-generated block randomization method with a fixed block size of four, implemented through a sealed-envelope web-based randomization system to ensure allocation concealment. Allocation was concealed from patients; however, the radiation oncologists were aware of treatment allocation due to the nature of radiotherapy planning. Radiologic assessment of progression and recurrence patterns were independently performed by the radiation oncologists and neuroradiologists who were blinded to the treatment allocation (Figure 1). The primary endpoint was progression-free survival (PFS), while the secondary endpoints included overall survival (OS) and recurrence pattern.

Workup and Treatment

Eligible patients who met the inclusion criteria and provided written informed consent were randomized to join either the intervention or control group.

Baseline assessments included complete blood count, serum biochemistry, immunohistochemistry (IHC), as well as a comprehensive medical history and physical examination. IHC was used to assess IDH1 R132H mutation status; also, MGMT promoter methylation was evaluated using molecular techniques. All patients underwent preoperative brain MRI, including gadolinium-enhanced T1-weighted and T2/FLAIR sequences.

As proton therapy was not available, all patients received photon-based radiotherapy. CT simulation was performed with patients immobilized using a thermoplastic mask. Based on tumor location, proximity to critical structures, equipment availability, and physician discretion, either 3D-CRT or intensity-modulated radiotherapy (IMRT) was used; however, most patients were treated with 3D-CRT due to resource limitations. Treatment planning was performed using PROWESS or ISOgray software.

In the control group, treatment followed the RTOG protocol using a two-phase approach to a total dose of 60 Gy. In the first phase, a 2-cm margin around the T2/FLAIR abnormality defined the CTV receiving 46 Gy. In the second phase, a 2-cm margin around the tumor

Table 1. summary of Target Delineation Guidelines

protocol	Technique	GTV	CTV	PTV	Dose
NRG [12]	2 phases	1st phase: Tumor bed+ residue[a]+ surrounding edema[b] Boost phase: Tumor bed+ residue[a]	GTV+2 cm GTV+2 cm		46 Gy Additional 14 Gy (60Gy)
ESTRO-EANO [13]	1 phase	Tumor bed+ residuea	GTV+ (2-3 cm)	CTV+ (5-7 mm)	60 Gy
ESTRO-EANO [14]	1 phase	Tumor bed+ residuea	GTV+ (1.5 cm)		60 Gy
ABTC [10]	2 phases	Tumor bed+ residuea+ surrounding edemab Tumor bed+ residuea	GTV+5mm GTV+5mm	GTV+5mm CTV+(3-5mm)	46 Gy Additional 14 Gy (60Gy)
MD ACC [11]	2 phases	Tumor bed+ residuea	GTV+2 cm GTV+0.5 cm		40 Gy Additional 20 Gy (60Gy)

[a], enhancing lesion on T1-weighted sequence MRI with gadolinium; [b], hypersignal lesion on T2-weighted sequence MRI

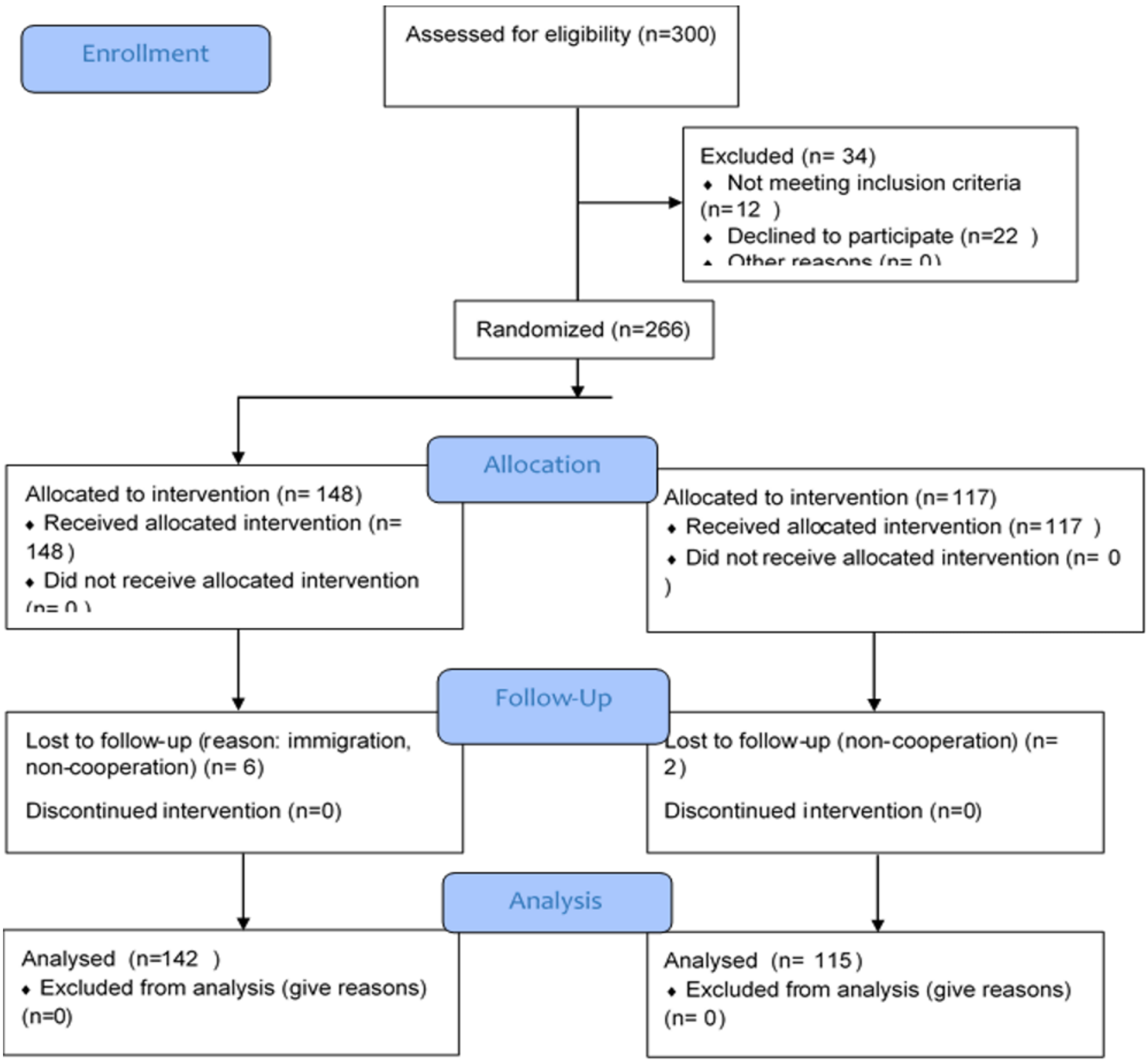

Figure 1. Protocol Flow Diagram

bed, surgical cavity, and contrast-enhancing regions on gadolinium-enhanced T1-weighted MRI defined the CTV receiving 60 Gy. The planning target volume (PTV) was generated by expanding the CTV by 5-7 mm to account for setup and motion uncertainties.

Similarly, in the intervention group, a similar two-phase approach was used, but with a reduced margin of 1 cm in both phases. All dose prescriptions were complied with International Commission on Radiation Units and Measurements (ICRU) Report No. 83.

Patients with grade 4 gliomas received concurrent chemoradiation with daily temozolomide (TMZ) at 75 mg/m², with weekly clinical assessments and complete blood counts during the treatment. Following chemoradiotherapy, patients received six cycles of adjuvant TMZ (150–200 mg/m²), initiated 4-6 weeks after completion of radiotherapy. Extension beyond six cycles was left to the treating physician due to limited evidence supporting prolonged therapy [26, 27].

For grade 3 astrocytoma, treatment consisted of adjuvant radiotherapy followed by 12 cycles of adjuvant TMZ (150–200 mg/m²), according to the CATNON trial protocol. Patients with grade 3 oligodendroglioma received six cycles of PCV chemotherapy, applying lomustine (110 mg/m² on day 1), procarbazine (60 mg/m² on days 8–21), and vincristine (1.4 mg/m², maximum 2 mg) on days 8 and 29, repeated every 42 days.

Follow-Up

Unlike other solid tumors such as breast cancer, where predictive biomarkers are available [15], high-grade gliomas lack reliable markers; making imaging surveillance essential. After completion of chemoradiotherapy, patients underwent physical examinations and gadolinium-enhanced brain MRI every 3–4 months during the first year and every 6 months thereafter. Imaging was compared with prior studies to assess disease status. Radiographic progression was defined according to the Macdonald criteria and confirmed independently by a radiation oncologist and a neuroradiologist. In cases of confirmed progression on gadolinium - enhanced T1-weighted MRI, images were fused with the original CT simulation in the treatment planning system. The enhancing recurrent tumor was contoured, and its volume was evaluated relative to the 95% isodose line. Recurrence patterns were classified as in-field (>80% of recurrence volume within the 95% isodose), marginal (20–80%), or out-field (<20%).

Table 2. Studies on High Grade Glioma Target Volume Delineation

Author	N	Study design	GTV	CTV	PTV	Dose [Gy]/Fx	Recurrence pattern	mPFS month	mOS month
Gebhardt et al.[10]	95	R	first phase: T1 enhancing and nonenhancing tumour volume (T2 or FLAIR) boost: T1 enhancing tumour volume	GTV + 5 mm	CTV + 3-5 mm	46/23 14/7	81% in-field 6% marginal 28% distant	8	-
Azoulay et al. [21]	30	RCT	tumour resection cavity, residual enhancing tumour, and nodular nonenhancing tumour	GTV + 5 mm	CTV + 0	25/5 30/5 35/5 40/5		8.2	14.8
Kumar et al. [11]	50	RCT	RTOG protocol tumour resection cavity + residual enhancing tumour MDACC protocol tumour resection cavity + residual enhancing tumour	Initial phase GTV + oedema + 20 mm boost GTV + 25 mm initial phase GTV + 20 mm boost phase GTV + 5 mm	CTV + 5 mm CTV + 5 mm	40/20 20/10 40/20 20/10	87% in-field 12.5% marginal 0% distant 87% in field 6.2% marginal 6.2% distant	6.1 8.8	12 17
Brown et al. [25]	67	RCT	tumour cavity and any residual T1 tumour enhancement	GTV + 20 mm	CTV + 3-5 mm GTV + 3-5 mm	60 /30 IMRT 60 /30 protons		8.9 6.6	21.2 24.5
Tu et al.[23]	68	R	tumour resection cavity + residual enhancing tumour	GTV + 20 mm	CTV + 5 mm	60 /30	100% within 2 cm from GTV, 94.8% within 1 cm	7	13
Zheng et al. [24]	55	R	tumour resection cavity + residual enhancing tumour	GTV + 10 mm GTV + 20 mm	CTV1 + 3 mm CTV2 + 3 mm	60/30 54/30	44pts central 2pts in-field 1pt marginal 1pt distant	7	17.7
Perry et al. [22]	562	RCT	tumour resection cavity + residual enhancing tumour	GTV + 15 mm	CTV1 + 3 mm CTV2 + 3 mm CTV + 5 mm	40/15		5.3	9.3

Statistical Analysis

Sample size calculation was based on PFS as the primary endpoint. A minimum of 96 patients per group was required to achieve 80% power at a 95% confidence level to detect a hazard ratio difference of 0.1, using PASS software.

Analyses were performed on an intention-to-treat basis. Kaplan–Meier methods were used to estimate PFS and OS, with comparisons made using the log-rank test. Cox proportional hazards models were applied to adjust for prognostic factors. Binary logistic regression was used to evaluate recurrence patterns and control for confounders. Variables with a p-value <0.2 in univariate analyses were included in multivariable models.

Categorical variables were analyzed using the chi-square or Fisher's exact test, and continuous variables using the Mann–Whitney U or Kruskal–Wallis tests. OS was calculated from the date of diagnosis (surgery) to death or last follow-up, and PFS from diagnosis to radiographic progression or last imaging assessment.

Results

A total of 258 patients with grade 3 and 4 gliomas were included. Of these, 75.6% had grade 4 gliomas, and 55.4% were allocated to the intervention group. Median follow-up from surgery was 14.5 months, and the median age was 55.5 years.

Baseline qualitative and quantitative characteristics are summarized in Tables 3 and 4. The two groups were well balanced with respect to sex, age, IDH mutation status, radiotherapy technique, extent of surgical resection (gross total resection, subtotal resection, or biopsy), interval between surgery and radiotherapy, chemoradiation tolerance, duration of adjuvant chemotherapy, and use of bevacizumab for disease progression.

Median GTV60 volume was 36.5 cm^3 and 23 cm^3 in the intervention and control groups, respectively ($p = 0.374$). Also, median GTV46 was 93.8 cm^3 and 51.4 cm^3 in the intervention and control groups, respectively ($p = 0.052$).

Imaging progression occurred in 87 patients (33.7%), 94% of whom had grade 4 gliomas. Progression was observed in 35% of patients in the intervention group and 32.2% in the control group ($p = 0.637$) [Table 5]. In-field recurrences accounted for 84% and 83.8% of cases in the intervention and control groups, respectively ($p = 0.829$).

However, binary logistic regression analysis demonstrated no significant difference in the risk of non–in-field recurrence between groups (HR = 0.896, 95% CI: 0.268–2.995; $p = 0.858$). Also, grade 3 gliomas

Table 3. Qualitative Variables Distribution in Study Groups

Variable		Intervention Number (%)	Control Number (%)	P value
Radiotherapy technique	3DCRT	127 (88.8)	105 (91.3)	0.508
	IMRT	16 (11.2)	10 (8.7)	
sex	Male	88 (61.5)	69 (60)	0.801
	Female	55 (38.5)	46 (40)	
Histology	Grade 4	116 (81.2)	79 (68.7)	0.028
	Grade 3	27 (18.8)	36 (31.3)	
IDH mutation (in assessed specimens)		20 /36 (55.6)	30 / 46 (65.2)	0.494
Surgery	Gross total resection	20 (14.1)	9 (7.8)	0.148
	Sub Total Resection	109 (76.2)	99 (86.1)	
	Biopsy Only	14 (9.9)	7 (6.1)	

showed a non-significant trend toward increased non–in-field recurrence (HR = 2.633, 95% CI: 0.383–18.10; p = 0.325). In addition, larger CTV volumes were not significantly associated with non–in-field recurrence (HR = 1.004, 95% CI: 0.999–1.008; p = 0.097).

At a median follow-up of 14.5 months, median OS in the intervention group was 22.0 ±2.98 months. But median OS was not reached in the control group (HR;1.517, 95%CI: 0.99-2.33, Pvalue:0.057). Survival curves are shown in Figure 2. When stratified by grade, median OS for grade 4 glioma was 19 and 23 months in the intervention and control groups (p = 0.042; Exp(B) = 1.483). But median OS for grade 3 glioma was not reached in either group [Table 6].

Also, median PFS was 15 ± 1.25 months in the intervention group, but it was 19 ± 2.712 months in the control group (HR; 1.32, 95%CI; 0.93-1.87, p = 0.121) [Table 7]. Finally, dose constraints for organs at risk

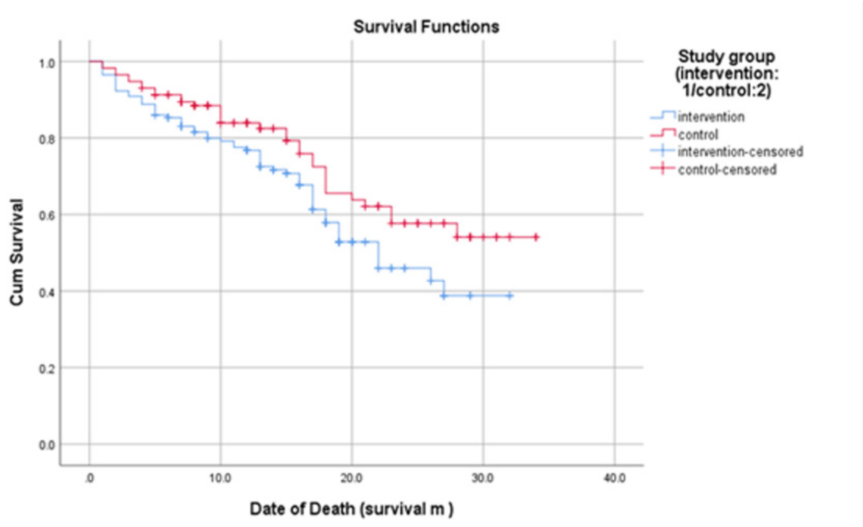

Figure 2. Survial Curve of Study Arms

Table 4. Quantitative Variables Distribution in Study Groups

Variable	Intervention		Control		P value
	mean±SD[a]	Median(IQR[b])	mean±SD[a]	Median(IQR[b])	
Surgery-radiotherapy interval (day)	39.38±20.6	35 (20)	43.34±28.36	41 (22)	0.152
Age	54.16 ±11.27	56 (14)	56.64±11.49	59.5 (14)	0.959
GTV 60 (cm^3)	59.70± 51.94	36.5 (67.2)	42.99±41.26	23 (41.25)	0.374
GTV 46 (cm^3)	113.36 ±91.9	93.8 (132)	86.77 ± 72	51.4 (89)	0.052
CTV 60 (cm^3)	140.33 ± 103.7	93.6 (168.9)	124.12 ± 127.55	140.1 (210.2)	0.047
CTV 46 (cm^3)	201.6± 157	189.4 (270)	210.5 ± 171.3	210.65 (304)	0.46
Duration of adjuvant chemotherapy (months)	5.73 ± 3.31	6 (2)	5.19 ± 2.52	6 (2)	0.165

[a], standard deviation; [b], Interquartile range

Table 5. Recurrence Distribution in Study Groups

Group	Intervention			Control			p-value
Outcome	Number(%)			Number(%)			
Imaging progression occurrence	50 (35.0)	Grade 3	3	37 (32.2)	Grade 3	2	0.637
		Grade 4	47		Grade 4	35	
Recurrence pattern	In-field	42 (84)		31 (83.8)			0.829
	Marginal	4 (8)		8 (9.2)			
	Out-field	4 (8)		2 (5.4)			

Table 6. Overall Survival of Study Groups

	Mean (months)		Median (months)		OS 1y (%)	OS 2y (%)	HR (95%CI)	P value
	±SE[a]	(95%CI)	±SE	(95%CI)				
Intervention	20.989 ±1.031	18.97-23.00	22 ±2.976	16.17-27.83	76.8	46	1.517 (0.99-2.33)	0.057
Control	25.08 ±1.231	22.67-27.49	-	-	83.9	57.7	1	
Total	23.22 ±0.838	21.577-24.86	-	-	79.9	51.1		

[a], standard error

(OARs) are presented in Table 8.

Discussion

In this prospective randomized trial, we evaluated whether reducing the CTV margin from 2 cm to 1 cm in patients with high-grade gliomas affected recurrence patterns or survival outcomes. It was found that reducing the CTV margin from 2 cm to 1 cm in the adjuvant radiotherapy of high-grade gliomas did not significantly affect progression-free survival, overall survival, or recurrence patterns. Below we will discuss the findings in detail with reference to some earlier studies.

The primary endpoint, PFS, did not differ significantly between the two groups (HR: 1.32, p = 0.121). Although OS was numerically inferior in the intervention group, this difference did not reach statistical significance (HR: 1.517, p = 0.057). Importantly, this finding must be interpreted in the context of baseline imbalances between treatment arms.

A higher proportion of patients in the intervention arm were found to have grade 4 gliomas and larger tumor

Table 7. Progression Free Survival of Study Groups

	Mean (months)		Median (months)		HR (95%CI)	P value
	±SE[a]	(95%CI)	±SE	(95%CI)		
Intervention	17.035 ±1.009	15.057-19.013	15 ±1.248	12.55-17.45	1.32 0.93-1.87	0.121
Control	19.48 ±1.18	17.16-21.81	19 ±2.712	13.68-24.31	1	
Total	17.99 ±0.77	16.49-19.50	16	13.41-18.6	-	

[a], standard error

Table 8. Comparison of OAR Doses between Intervention and Control Groups (Mann-Whitney U test)

OAR	Intervention (median)	Control (median)	Asymp. Sig. (2-tailed)
Tumor-side optic nerve max dose (GY)	34.06	44	0.130
Contralateral optic nerve max dose (Gy)	15.17	19	0.009*
Chiasm max (Gy)	42.35	33	0.113
Brainstem max (Gy)	48.20	31.75	0.534
Tumor-side cochlea mean dose (Gy)	15.95	2.98	0.699
Contralateral cochlea mean dose (Gy)	5.13	1.5	0.525
Tumor-side hippocampus V7(%)	56.5	21.5	0.874
Contralateral hippocampus V7(%)	50.5	16	0.880

volumes (GTV46 and GTV60), both of which are well-established adverse prognostic factors in high-grade gliomas. Although the difference in GTV46 narrowly missed statistical significance ($p = 0.052$), it is likely to be clinically relevant. Given the strong prognostic influence of tumor burden and histologic grade, these factors may have outweighed the effect of CTV margin reduction. Tumor volume and geometric characteristics have been consistently associated with poorer outcomes [28–30], and achieving perfect stratification by tumor burden in randomized trials remains challenging. These imbalances likely contributed to the numerically inferior OS observed in the intervention arm and may have outweighed any effect of CTV margin reduction. Additionally, a higher proportion of patients in the intervention group had grade 4 gliomas, which are associated with worse outcomes than grade 3 gliomas. Furthermore, in the molecular era of neuro-oncology, several molecular alterations influence prognosis [31]; however, comprehensive molecular profiling was not feasible for all patients due to limited resources.

Although the majority of patients in this study were treated using 3D-CRT, which is less conformal than IMRT or VMAT, our findings suggest that margin reduction to 1 cm is feasible even with conventional techniques. While IMRT and VMAT offer superior dose conformity and improved normal tissue sparing, particularly of the brainstem and optic apparatus [32,33], 3D-CRT remains widely used in resource-limited settings. Therefore, the results of this study may be particularly relevant for centers transitioning from 3D-CRT to more advanced radiotherapy techniques

The extent of surgical resection is another critical prognostic factor. Supramaximal resection, which is defined in some surgical series as the removal of the contrast-enhancing tumor on T1-weighted MRI plus approximately 1 cm of surrounding non–contrast-enhancing brain tissue, has been associated with improved survival in HGGs [34, 35]. In this cohort, gross total resection was achieved in a minority of patients (14.1% in the intervention group and 7.8% in the control group), with most having residual disease or undergoing biopsy alone. In such cases, tumor progression may be driven more by residual disease burden than by differences in radiotherapy margins, potentially confounding the recurrence analyses.

Regarding doses to organs at risk (OARs), reducing treatment volume aims to limit radiation exposure to normal brain tissue and mitigate toxicity. This consideration is particularly relevant given the growing interest in re-irradiation for recurrent HGGs [36]. Although larger tumors in the intervention group were expected to result in higher doses to organs at risk, margin reduction was associated with a statistically significant reduction in the maximum dose to the contralateral optic nerve. While median doses to other organs at risk were higher in the intervention group, these differences were not statistically significant, suggesting a potential dosimetric benefit of margin reduction.

Historically, ESTRO-ACROP, EORTC, and RTOG guidelines recommended a 2-cm GTV-to-CTV margin, based on evidence that over 80% of recurrences occur within this distance [37]. However, most recent studies have evaluated smaller margins (0.5–1.5 cm) using various fractionation schemes and planning approaches, with comparable outcomes in terms of OS, PFS, and recurrence patterns [8, 9, 25–32]. As these data were not fully incorporated into earlier guidelines, our study was designed to prospectively assess the safety of a 1-cm margin. Notably, the most recent ESTRO-ACROP guideline now recommends a 1.5-cm margin [14].

Despite its limitations, this trial provided remarkable real-world evidence from a resource-limited setting. The lack of significant differences in PFS and OS should be interpreted cautiously, particularly given the imbalance in histological grades between the study arms. The strengths of this study include its prospective design, relatively large sample size, and pragmatic focus. Further studies incorporating modern radiotherapy techniques, standardized surgical strategies, and comprehensive molecular stratification are warranted to better define the impact of margin reduction on tumor control, neurotoxicity, and quality of life.

Conclusion and Limitations

In accordance with recent international guidelines, particularly those from ESTRO-ACROP, reduced radiotherapy margins in high-grade gliomas appear safe and feasible. Our findings support this approach, demonstrating that a smaller CTV margin does not significantly alter recurrence patterns in the context of predominantly 3D-CRT-based treatment and limited surgical resection. However, conclusions regarding overall survival should be interpreted with caution. Longer follow-up and comprehensive molecular characterization, including IDH mutation and MGMT promoter methylation status, are required to fully elucidate survival differences between treatment groups.

Author Contribution Statement

Experimental design: (KA, SAJ), acquisition: (PR, SAJ, DF, MD, BG), analysis: (HE), interpretation: (SAA, SSH, SAJ, PR, BG). All authors have been involved in the writing of the manuscript and approved the final version.

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Data availability statement

All data gathered and analyzed during this study can be accessed through direct communication with the corresponding author and the agreement of all research team members.

Ethical approval statement

The protocol of the study was approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1399.711); and a written informed consent was obtained from the patients or their legal guardian.

RCT registration code

We do confirm that the trial has been registered prospectively on Iranian Registry for Clinical Trials (IRCT) with Clinical trial registration number: IRCT20210215050367N1 and Protocol Date 2021-03-6.

Conflict of interest

None to declare

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