

Hypofractionated vs. Conventionally fractionated Radiotherapy in the Treatment of Glioblastoma: A Prospective, Randomized Comparative Study

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Abstract

Background: Glioblastoma are aggressive primary brain tumors associated with poor prognosis despite multimodality treatment. Hypofractionated radiotherapy (HFRT) has emerged as an alternative to conventionally fractionated radiotherapy (CFRT), particularly in elderly or poor-performance patients. This study compared the efficacy, toxicity, and quality-of-life outcomes of HFRT versus CFRT in patients with poor-prognosis high-grade gliomas.

Materials and Methods: In this prospective randomized study, 21 patients with newly diagnosed high-grade gliomas belonging to RPA class IV–VI were enrolled between November 2017 and June 2019. Patients were randomized to receive either HFRT (40 Gy in 15 fractions over 3 weeks; n=10) or CFRT (60 Gy in 30 fractions over 6 weeks; n=11). All patients received concurrent and adjuvant temozolomide. Primary endpoint was overall survival (OS), while secondary endpoints included progression-free survival (PFS), toxicity, and quality of life (QoL). Treatment response and prognostic factors were analyzed using Cox regression models.

Results: Median PFS was 4.99 months in the HFRT arm and 7.0 months in the CFRT arm ($p=0.497$). Median OS was 12.5 months with HFRT and 5.8 months with CFRT ($p=0.079$). No grade 3–4 haematological toxicities were observed in either arm. QoL outcomes were comparable between groups, with fewer significant symptom deteriorations in the HFRT arm. Pre-treatment RPA class was identified as an independent prognostic factor for OS ($p=0.014$).

Conclusion: HFRT demonstrated comparable survival, acceptable toxicity, and preserved QoL compared with CFRT in glioblastoma patients with poor prognosis, supporting its use as a practical treatment option in selected patients.

Keywords: Glioblastoma, Hypofractionated Radiotherapy, High-Grade Glioma, Quality of Life, Temozolomide

Introduction:

Glioblastoma (GBM) is the most common and aggressive primary brain tumor in adults. Despite advances in treatment, the prognosis for patients with GBM remains poor, with a median survival of only 15–17 months¹ in those who receive contemporary treatment. The 5-year survival rate is mere 7.2%.¹ Standard treatment for GBM typically includes maximal safe surgical resection followed by radiotherapy (RT) with concomitant and adjuvant chemotherapy. However, even with aggressive treatment, many patients experience disease recurrence and ultimately succumb to the disease.

In the recent years, hypofractionated radiotherapy (HFRT) has been established as a promising alternative to standard

conventionally fractionated RT^{2,3} in the treatment of high-grade gliomas, including GBM, particularly in elderly patients (≥ 65 years), patients with poor performance status (KPS < 70) and frail patients unable to tolerate 6 weeks of RT.² HFRT involves the delivery of a higher dose of radiation per fraction, over a shorter period of time, compared to conventional RT (60 Gray in 30 fractions over 6 weeks). Perry et al., showed that the addition of Temozolomide (TMZ) to HFRT increases the survival benefit similar to the concurrent standard RT and TMZ.⁴

Several studies have evaluated the efficacy and safety of HFRT in the treatment of high-grade gliomas, including GBM.^{4,5} Arvola et al.,⁶

found that HFRT was associated with similar overall survival and progression-free survival outcomes as conventional RT in patients with high-grade gliomas. These findings have been supported by a recent meta-analysis,⁷ which found no significant differences in overall survival, progression-free survival, or treatment-related toxicities between HFRT and conventional RT in patients with high-grade gliomas.

Despite these promising results, some clinicians have raised concerns about the potential for HFRT to increase the risk of treatment-related toxicities, such as radiation necrosis. In addition, there are currently no standardized guidelines for the use of HFRT in the treatment of high-grade gliomas beyond elderly population, and further studies are needed to determine the optimal dosage and fractionation schedules for this approach. This study was carried out to evaluate the efficacy and safety of HFRT as compared to conventional RT in patients with high-grade gliomas, specifically those with poor prognoses, including those with GBM.

Materials and Methods

The study population consist of newly diagnosed patients with high-grade gliomas who visited the radiotherapy outpatient department at our center between November 2017 and June 2019.

Inclusion Criteria

Histologically proven cases of high-grade gliomas belonging to RPA class IV-VI with normal hematological, renal, and hepatic functions were included in the study after obtaining written informed consent.

Exclusion Criteria

Patients with a previous history of RT to the brain, history of any chemotherapy, and transformed low-grade gliomas were excluded from the protocol.

The patients were randomized into the HFRT arm and standard RT arm by using a table of random digits. All the patients underwent pretreatment workup following maximal safe resection of the tumor which included a complete history and physical examination, surgical details documentation, neurological performance status (NPS) and Karnofsky performance status (KPS) documentation, quality of life assessment before start of RT, and contrast-enhanced Magnetic Resonance Imaging (MRI) brain.

Radiotherapy Technique

The patients were treated with Intensity Modulated Radiotherapy (IMRT) technique on a 6 MV linear accelerator. All the patients were simulated in the supine position and immobilized with a three-clamp thermoplastic cast. Contrast-enhanced Computed Tomography (CECT) images were obtained from the vertex to the base of the skull with a 2.5 mm slice thickness and transferred to the treatment planning system (TPS). Postoperative MRI brain images were then registered with planning CT images, and target delineation was done based on ESTRO-ACROP guidelines (2016)⁸ for target delineation of glioblastoma. In the HFRT arm, the dose prescription was 40 Gy in 15 fractions over 3 weeks, while patients in the conventionally fractionated arm was 60 Gy in 30 fractions over 6 weeks.

Concurrent and Adjuvant Temozolomide (TMZ)

TMZ was administered concurrently with RT at a dose of 75mg/m² throughout the treatment. Additionally, 6 cycles of adjuvant TMZ were given at a dose of 150-200mg/m² for five consecutive days as 28 days cycle following a gap of 4 weeks after completion of RT.

Response Assessment

Patients were monitored during treatment with weekly clinical assessment and complete blood count. Acute hematological toxicities were recorded as per RTOG toxicity criteria. After completion of treatment, patients were on monthly follow-up, and a response assessment MRI brain was done after 3 months of completion of RT and if clinically indicated thereafter. The patients were assessed for quality of life (QoL) using the EORTC QLQ-30 questionnaire and Brain Cancer module (BN-20).

Statistical Analysis

The endpoints were measured from the date of surgery for overall survival (OS), and completion of RT for progression-free survival (PFS) and follow-up. Patients dying of any cause or progression of disease or lost to follow-up were considered as events for both the endpoints of progression-free and overall survival. The primary endpoint was OS, while secondary endpoints were PFS and QoL. Radiological evidence was used to evaluate that the disease has progressed. Differences in proportions in patient disease and treatment characteristics were tested by the χ^2 test, while differences in means were tested by the t-test. Univariate and multivariate analyses were done using the Cox regression method. All statistical computations were done using SPSS version 16.

Observations and Results

A total of 21 previously untreated patients with glioblastoma were enrolled in the study; of these, 10 patients were randomised to the HFRT arm, and 11 patients to the standard RT arm. Baseline patient and treatment characteristics were generally well balanced between the two groups, except for KPS and NPS, with a significantly higher proportion of patients having poorer performance status in the HFRT arm. The overall duration of RT was significantly shorter in the HFRT arm compared with the standard RT arm ($p = 0.024$).

RT could not be completed to the planned dose in one patient in the HFRT arm and in two patients in the standard RT arm. Among these three patients, one patient in each arm voluntarily discontinued treatment, while in one patient in the standard RT arm, RT was terminated at a total dose of 56 Gy at the discretion of the physician in order to limit the dose to the brainstem. Detailed patient and treatment characteristics are summarized in Table 1. Concurrent TMZ administered with RT was well tolerated in both treatment arms, and no Grade 3 or 4 acute haematological toxicities were observed (Table 2). None of the patients experienced episodes of raised intracranial tension during treatment. Alopecia was universal among treated patients. Following completion of chemoradiation, a slight improvement in KPS and NPS was observed in both arms; however, these changes were not statistically significant in either group (Table 3).

The median follow-up duration was 2.3 months (range: 0.13–19.1 months) for the HFRT arm and 4.3 months (range: 0.72–18.8 months) for the standard RT arm. The median PFS in the HFRT arm and standard arm were 4.99 and 7.0 months, respectively ($p = 0.497$). The median OS was 12.5 months in the HFRT arm and 5.8 months in the standard RT arm ($p = 0.079$), as shown in Figure 1.

An exploratory univariate analysis was performed to identify patient-, disease-, and treatment-related factors potentially influencing PFS and OS. Variables found to be significant on univariate analysis were subsequently included in a multivariate Cox regression model, which demonstrated that pre-RT RPA class was a significant predictor of OS ($p = 0.014$), as detailed in Tables 4 and 5.

Table 1: Patient and Treatment Characteristics

Characteristics (Total n = 21)		Standard RT arm (n = 11)	HFRT arm (n = 10)	p value
Median Age in years (range)		53 (15-67)	50 (20-68)	0.575
Sex	Male	6 (54.5%)	8 (80%)	0.221
	Female	5 (45.5%)	2 (20%)	
Median Symptoms duration in months (range)		4 (1-11)	4.5 (1-18)	0.462
KPS (Before RT)	40-50	2 (18.2%)	8 (50%)	0.017
	60-70	5 (45.5%)	1 (10%)	
	≥ 80	4 (36.4%)	1 (10%)	
NPS (Before RT)	1	8 (72.7%)	1 (10)	0.015
	2	1 (9.1%)	3 (30)	
	3	2 (18.2%)	6 (60)	
RPA (Before RT)	IV	10 (90.9%)	5 (50%)	0.060
	V-VI	1 (9.1%)	5 (40%)	
Extent of Surgery	Decompression	2 (18.2%)	1 (10%)	0.514
	Debulking	1 (9.1%)	0	
	Subtotal	0 (0)	1 (10%)	
	GTR	8 (72.7%)	8 (80%)	
Median Gap Surgery to RT (weeks)		6.8 (4.4-20.4)	10.07 (6-18.4)	0.119
Radiation received	Complete	9 (81.8%)	9 (90%)	0.538
	Incomplete	2 (18.2%)	1 (10%)	
Median RT duration in days (range)		45 (29-52)	19 (15-22)	0.024

Table 2: Acute Hematological Toxicity

Grade of Toxicity		1 st week	2 nd week	3 rd week	4 th week	5 th week	6 th week
Standard RT (n = 11)	Gr 1	0	0	3 (27.3%)	4 (36.4%)	3 (27.3%)	4 (36.4%)
	Gr 2	0	0	0	1 (9.1%)	1 (9.1%)	1 (9.1%)
	Gr 3-4	0	0	0	0	0	0
HFRT (n = 10)	Gr 1	1 (10)	1 (10)	0	-	-	-
	Gr 2	0	0	1 (10)	-	-	-
	Gr 3-4	0	0	0	-	-	-

Table 3: Response to Treatment

Parameters		Standard RT	HFRT	p-value
Change in KPS (post RT- pre-RT)	Improved	2 (18.2%)	3 (30%)	0.149
	Unchanged	2 (18.2%)	2 (20%)	
	Deteriorated	7 (63.6%)	5 (50%)	
Change in NPS (post RT- pre-RT)	Improved	5 (45.5%)	4 (40%)	1.000
	Unchanged	5 (45.5%)	4 (40%)	
	Deteriorated	1 (9.1%)	2 (20%)	

QOL analysis revealed that patients in the standard RT arm experienced significant changes in physical functioning scores. In addition, fatigue, pain, financial difficulties, communication deficits, and pruritus showed significant differences between pre- and post-RT assessments in this arm. In contrast, patients in the HFRT arm demonstrated significant changes only in pain and constipation scores.

QoL analysis showed that the patients in the standard RT arm had significant changes in the physical functional score. Additionally, in this arm, parameters such as fatigue, pain, financial

difficulties, communication deficit, and itching showed significant differences between pre- and post-RT scores. Patients in the HFRT arm showed significant changes in pain and constipation scores.

Discussion

Glioblastoma is an aggressive primary brain tumor associated with a poor prognosis despite advances in multimodality treatment. Current standard of care for fit patients with good performance status consists of maximal safe surgical resection followed by

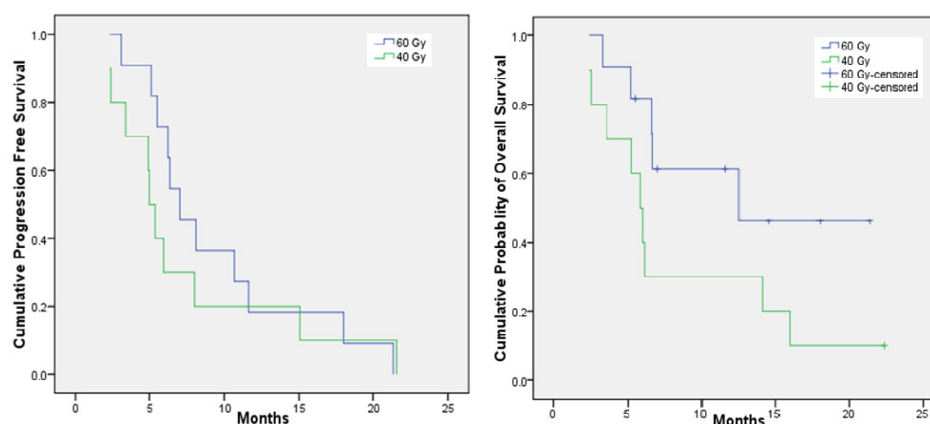


Figure 1: Progression free survival and Overall survival

Table 4: Cox Regression Univariate and Multivariate Analysis of Prognostic Factors for Progression Free Survival

Variables		Univariate			Multivariate		
		HR	95%CI	p-value	HR	95%CI	p-value
Age	<50 vs ≥50 years	0.342	0.132-0.888	0.028	0.265	0.060-1.164	0.079 (NS)
Sex	Male vs Female	1.272	0.495-3.267	0.618	-	-	-
Symptom Duration	<6 vs ≥6 months	1.595	0.631-4.030	0.323	-	-	-
Extent of Resection	Gross/ Subtotal vs Decompression/ Debulking	0.889	0.288-2.749	0.839	-	-	-
Pre RT KPS	≥70 vs < 70	0.250	0.094-0.666	0.006	0.262	0.019-3.578	0.315 (NS)
Pre RT RPA	IV vs V+VI	0.052	0.010-0.273	0.000	0.272	0.034-2.171	0.219 (NS)
Pre RT NPS	1 vs 2/3	0.246	0.089-0.680	0.007	0.721	0.076-6.852	0.721 (NS)
Gap b/w surgery & RT	<8 vs ≥8 weeks	1.174	0.472-2.921	0.730	-	-	-
RT Schedule	Standard vs HFRT	0.736	0.302-1.791	0.499	-	-	-
Adjuvant TMZ	6 vs < 6 cycles	0.138	0.018-1.090	0.060	-	-	-

Table 5: Cox Regression Univariate and Multivariate Analysis of Prognostic Factors for Overall Survival

Variable		Univariate			Multivariate		
		HR	95%CI	p-value	HR	95%CI	p-value
Age	<50 vs ≥50 years	0.532	0.181-1.568	0.253	-	-	-
Sex	Male vs Female	1.478	0.506-4.313	0.475	-	-	-
Symptom Duration	<6 vs ≥6 months	1.115	0.385-3.229	0.842	-	-	-
Extent of Resection	Gross/ Subtotal vs Decompression/ Debulking	2.775	0.355-21.707	0.331	-	-	-
Pre RT KPS	≥70 vs < 70	0.132	0.036-0.486	0.002	0.000	0.000-3.986	0.935
Pre RT RPA	IV vs V+VI	0.029	0.003-0.253	0.001	0.064	0.007-0.575	0.014
Pre RT NPS	1 vs 2/3	0.171	0.047-0.625	0.008	3.428	0.000-2.05E	0.945
Gap b/w surgery & RT	<8 vs ≥8 weeks	0.779	0.242-2.502	0.674	-	-	-
RT Schedule	Standard vs HFRT	0.384	0.127-1.159	0.090	-	-	-
Adjuvant TMZ	6 vs < 6 cycles	0.031	0.000-11.623	0.250	-	-	-

conventionally fractionated radiotherapy (60 Gy in 30 fractions) with concurrent and adjuvant temozolomide, as recommended by both NCCN⁹ and EANO¹⁰ guidelines. The addition of temozolomide to adjuvant RT improves median OS by approximately 2.5 months¹¹ compared with RT alone. However, outcomes in patients with poor prognostic features, such as advanced age, poor performance status, unfavorable neurological function, and adverse recursive partitioning analysis (RPA) class, remain unsatisfactory, with substantially shorter survival compared with favorable-risk cohorts.

For patients with poor performance status or advanced age, both NCCN and EANO guidelines recognize hypofractionated radiotherapy as an appropriate alternative to standard six-week radiotherapy schedules. These recommendations are based on evidence demonstrating comparable survival outcomes with shorter treatment courses, reduced treatment burden, and acceptable toxicity profiles in selected patient populations.²⁻⁷ In this context, hypofractionated radiotherapy is primarily intended as a treatment de-intensification strategy rather than a means of improving oncological outcomes.

The rationale for hypofractionation in poor-prognosis glioblastoma is multifactorial. From a clinical perspective, shortening overall treatment duration reduces hospital visits, caregiver burden, and logistical challenges, thereby improving treatment feasibility and compliance in a population with limited life expectancy.¹² From a health-system standpoint, hypofractionation improves radiotherapy resource utilization, which is particularly relevant in high-volume centers and resource-constrained settings. While radiobiological considerations such as rapid tumor repopulation and relative radioresistance of glioblastoma have been proposed as potential justifications for larger fraction sizes, current clinical evidence supports non-inferiority rather than superiority of hypofractionated schedules.¹³

The findings of the present study are consistent with guideline-supported practice. The hypofractionated regimen of 40 Gy in 15 fractions over three weeks demonstrated quality-of-life outcomes comparable to those achieved with conventional fractionation. Although progression-free and overall survival were numerically lower in the hypofractionated arm, these differences were not statistically significant and are likely attributable to baseline imbalances in performance status, with a higher proportion of patients with poor Karnofsky and neurological performance status in this arm. Importantly, survival outcomes in both treatment groups were in line with historical outcomes reported for poor-prognosis glioblastoma patients treated according to guideline-accepted approaches. These results are concordant with several key studies that inform current recommendations.²⁻⁷ Randomized trials by Roa et al.,⁵ demonstrated similar survival outcomes between 40 Gy in 15 fractions and 60 Gy in 30 fractions in elderly glioblastoma patients. Other prospective and institutional studies evaluating various hypofractionated regimens have likewise shown comparable outcomes to conventional fractionation in elderly or poor-performance cohorts, without a clear increase in toxicity. Collectively, this body of evidence supports the use of hypofractionated radiotherapy as a standard option for selected patients, rather than as a replacement for conventional chemoradiation in fit individuals.

The selection of poor-prognosis patients in the present study is consistent with guideline-based risk stratification. Both NCCN and EANO emphasize the importance of patient-related factors, such as age, performance status, neurological function, and extent of resection, in determining treatment intensity. Patients

with favorable prognostic features, including good performance status and lower RPA class, derive greater benefit from standard fractionation with concurrent temozolomide and are therefore not ideal candidates for treatment shortening strategies. Restricting hypofractionation to poor-risk patients ensures appropriate alignment with contemporary standards of care. Target volume delineation using a single-phase approach in this study also reflects modern guideline recommendations. Both NCCN and EANO acknowledge that the majority of recurrences in glioblastoma occur locally, within or adjacent to the high-dose region. Consequently, contemporary contouring guidelines favor single-phase treatment strategies with appropriately defined margins rather than sequential shrinking-field techniques.

Quality of life is increasingly recognized as a critical endpoint in glioblastoma management, particularly for patients with limited survival. While survival remains the primary determinant of treatment selection, guidelines emphasize the importance of preserving neurological function and quality of life. The present study contributes to the limited prospective data in this area by demonstrating that hypofractionated radiotherapy does not compromise overall quality of life when compared with conventional fractionation in poor-prognosis patients.

Several limitations of the study must be acknowledged, including the small sample size and relatively short follow-up duration, which limit the assessment of long-term outcomes and late toxicity. Although no significant increase in treatment-related toxicity was observed, the potential for late radiation-induced brain injury with hypofractionated schedules remains a concern and underscores the need for careful patient selection and continued prospective evaluation.

Conclusion

In conclusion, hypofractionated radiotherapy represents a valid and effective treatment option for patients with poor-prognosis glioblastoma who are unsuitable for prolonged conventional chemoradiation. The comparable survival and quality-of-life outcomes observed in this study, together with the advantages of shorter treatment duration and reduced treatment burden, support the integration of hypofractionation into routine clinical practice for appropriately selected patients. Conventionally fractionated chemoradiation, however, remains the standard of care for fit patients with favorable prognostic features.

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How to cite this article: Ranjan R, Choudhary S, Aggarwal LM, Singh S, Sakthivel S, Nandi D, Gupta N, Singh R, Ranjan R, Mani N. Hypofractionated vs. Conventionally fractionated Radiotherapy in the Treatment of Glioblastoma: A Prospective, Randomized Comparative Study. *Journal of Cancer Diagnosis and Therapeutics*. 2026;1(1):22-27.

Source of support: Nil

Conflict of interest: None