Original Article

Moderately Hypofractionated Concurrent Chemoradiotherapy for High-Grade Glioma: A Prospective Observational Study of Early Response and Treatment Toxicity

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Abstract

Background: High-grade gliomas (HGG) are aggressive primary brain tumours with poor outcomes despite multimodal treatment. Hypofractionated radiotherapy may shorten treatment duration while maintaining clinical effectiveness. This study evaluated the early radiological response, treatment tolerability, and haematological toxicity of hypofractionated concurrent chemoradiotherapy in adults with HGG. **Material and Methods:** This prospective observational study included 30 patients aged 21-59 years with histologically confirmed HGG treated at a tertiary care centre. Patients underwent surgery followed by hypofractionated radiotherapy delivering 58.5 Gy in 25 fractions over 5 weeks, with concurrent temozolomide at 75 mg/m2/day. Adjuvant temozolomide was subsequently administered at 150-200 mg/m2 for 5 days every 28 days. Radiological response was assessed using contrast-enhanced MRI classified according to RECIST version 1.1. Toxicities were graded according to the Common Terminology Criteria for Adverse Events version 5.0. **Results:** The proportion of lesions measuring <2 cm increased from 23.3% at baseline to 73.3% at 3 months ($p<0.0001$). At 3 months, 3.3% of patients had a near-complete response, 20.0% had a partial response, 73.3% had stable disease, and 3.3% had progressive disease. Treatment was well tolerated, with no grade 3-4 haematological toxicities, thrombocytopenia, treatment interruptions, or dose adjustments. Neurological symptoms remained infrequent during follow-up. **Conclusion:** Moderately hypofractionated concurrent chemoradiotherapy with temozolomide demonstrated encouraging early radiological response, excellent treatment compliance, and minimal acute toxicity in adults with HGG. Its shorter treatment duration may improve radiotherapy resource utilisation and reduce patient burden, particularly in resource-limited settings. Larger comparative studies with longer follow-up are needed to establish long-term survival and late toxicity outcomes.

Keywords: High-grade glioma; Hypofractionated radiotherapy; Concurrent chemoradiotherapy; Temozolomide; Radiological response; Treatment toxicity.

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Introduction

According to recent GLOBOCAN estimates, central nervous system (CNS) tumours rank nineteenth among cancers worldwide and are associated with substantial mortality. Gliomas account for more than half of primary CNS tumours, with high-grade gliomas representing the most aggressive subtype.[1] Despite advances in multimodal treatment, prognosis remains poor, with a median overall survival of approximately 15-17 months and a 5-year survival rate below 10%.[2] Although the aetiology remains incompletely understood, recognised risk factors include prior exposure to ionising radiation and certain occupational and environmental exposures, often with a latency period exceeding 10-20 years.

Advances in the understanding of glioma biology and molecular genetics have substantially reshaped tumour classification, culminating in the 2021 World Health Organization (WHO) Classification of Tumours of the CNS.[3,4] Molecular profiling now plays a central role in the diagnosis, classification, prognostication, and management of gliomas. Key molecular alterations include isocitrate dehydrogenase (IDH)-wild-type astrocytomas harbouring epidermal growth factor receptor amplification, concurrent gain of whole chromosome 7 and loss of whole chromosome 10, or telomerase reverse transcriptase promoter mutations.[5] O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation remains an important predictive biomarker, as methylated tumours demonstrate improved responsiveness to temozolomide. Younger age and better performance status are also among the strongest treatment-independent prognostic factors associated with favourable outcomes.[6]

Patients commonly present with seizures, focal neurological

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deficits, neurocognitive impairment, or symptoms of raised intracranial pressure.[7] Given their aggressive clinical behaviour, high-grade gliomas require multidisciplinary multimodal treatment. The current standard of care for glioblastoma comprises maximal safe surgical resection followed by postoperative radiotherapy with concurrent and adjuvant temozolomide.[8] Randomised trials have established the survival benefit of postoperative radiotherapy, which is generally initiated within 4-6 weeks after surgery and may begin as early as 2 weeks after biopsy in selected patients.[9,10] The landmark EORTC-NCIC trial established conventionally fractionated radiotherapy (60 Gy in 30 fractions over 6 weeks) with concurrent and adjuvant temozolomide as the standard treatment approach, improving 5-year overall survival from 2% to 10%.[2]

Radiotherapy remains a cornerstone of glioma management, with ongoing efforts to optimise fractionation while maintaining efficacy and minimising toxicity. The Canadian and Nordic randomised trials demonstrated comparable outcomes with moderate hypofractionated radiotherapy and conventional fractionation in selected elderly patients, while reducing treatment duration.[11,12] However, neither trial incorporated concurrent or adjuvant temozolomide, and robust randomised evidence comparing conventional and hypofractionated regimens in the setting of contemporary chemoradiotherapy remains limited. Hypofractionation may provide comparable efficacy, particularly in elderly patients and those with poor performance status, while reducing treatment burden and potentially limiting treatment-related lymphopenia.[13]

Limited radiotherapy infrastructure and increasing patient volumes place substantial pressure on oncology services, particularly in low- and middle-income countries. Shorter treatment schedules may improve access to radiotherapy by reducing overall treatment time and resource utilisation. Given the aggressive nature of high-grade gliomas and the need for timely postoperative treatment, hypofractionation may also represent a practical option for selected younger patients with good performance status.[13]

Evidence regarding hypofractionated radiotherapy for high-grade gliomas in India remains limited. Therefore, our institution implemented a moderately hypofractionated regimen that shortens treatment duration by one week compared with the conventional 6-week schedule while modestly increasing the dose per fraction. This approach may reduce hospital visits, travel-related and accommodation costs, caregiver burden, and treatment-related resource utilisation. Accordingly, the present study evaluated the early radiological response, treatment compliance, and acute toxicity of hypofractionated concurrent chemoradiotherapy with temozolomide in adults with high-grade glioma.

Materials and Methods

Study design and participants: This prospective, single-centre observational study was conducted in the Department of Radiation Oncology, Vardhaman Mahavir Medical College, over an 18-month period (January 2024 to August 2025). The study aimed to evaluate treatment response and treatment-related toxicities associated with hypofractionated concurrent chemoradiotherapy in patients with high-grade glioma. Ethical approval was obtained from the Institutional Ethics Committee before study initiation, and all participants provided written informed consent prior to enrolment.

Thirty consecutive patients with histologically confirmed high-grade glioma were prospectively enrolled following maximal safe surgical resection. Baseline evaluation included detailed clinical history, physical examination, postoperative contrast-enhanced magnetic resonance imaging (CEMRI), complete blood count, liver function tests, renal function tests, serum electrolytes, and random blood glucose estimation.

Eligibility criteria: Patients aged 28-60 years with histologically confirmed high-grade glioma and an Eastern Cooperative Oncology Group (ECOG) performance status suitable for radical chemoradiotherapy were eligible for inclusion. Patients with low-grade gliomas, recurrent disease, previous cranial irradiation, or those considered unsuitable for definitive treatment because of advanced age or poor performance status were excluded.

Treatment protocol: All patients received hypofractionated external beam radiotherapy with concurrent temozolomide. Radiotherapy was delivered to a total dose of 58.5 Gy in 25 fractions (2.34 Gy per fraction) over five weeks, administered once daily, five days per week.

Treatment planning consisted of two sequential phases. Phase I encompassed the gross tumour volume with surrounding peritumoural oedema and a 1.5-2 cm margin, receiving 44.5 Gy in 19 fractions. Phase II delivered a boost dose of 14 Gy in 6 fractions to the residual tumour or postoperative tumour bed, resulting in a cumulative dose of 58.5 Gy.

Concurrent temozolomide was administered orally at 75 mg/m² daily throughout radiotherapy. Following completion of chemoradiotherapy, patients received adjuvant temozolomide at 150-200 mg/m²/day for five consecutive days every 28 days, according to institutional protocol.

Outcome measures: The primary outcome was radiological treatment response following hypofractionated chemoradiotherapy. Tumour response was evaluated using contrast-enhanced magnetic resonance imaging at scheduled follow-up visits and classified according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).

Secondary outcomes included treatment-related haematological toxicities during concurrent chemoradiotherapy and the first three months of adjuvant temozolomide therapy.

Haematological parameters evaluated included anaemia, neutropenia, lymphopenia, and thrombocytopenia. Particular attention was given to clinically significant (grade ≥3) toxicities, treatment interruptions, dose modifications, and supportive interventions.

Follow-up and toxicity assessment: Patients were reviewed weekly throughout concurrent chemoradiotherapy to assess treatment compliance, clinical status, laboratory parameters, and acute adverse events. Scheduled follow-up visits were conducted at one and three months after completion of radiotherapy. Each visit included clinical examination, complete blood count, and assessment of treatment-related toxicities. Acute toxicities were

graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Additional clinical or radiological assessments were performed whenever clinically indicated.

Statistical analysis: Categorical variables were summarised as frequencies and percentages, whereas continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate. Fisher's exact test was used to compare categorical variables because of the small sample size and expected cell counts below five. Changes in paired categorical outcomes were analysed using the Bhapkar test. Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA), with data initially entered into Microsoft Excel.

Results

Patient characteristics: A total of 30 patients with histologically confirmed high-grade glioma were prospectively enrolled, completed the planned treatment, and were included in the final analysis. The baseline demographic, clinical, tumour, and treatment characteristics are summarised in Table 1. The mean age was 45.9 ± 10.9 years, with most patients (40.0%) aged 51-60 years. Males constituted 80.0% of the cohort, and most patients (83.3%) had no associated comorbidities. Headache (50.0%) and seizures (33.3%) were the most common presenting symptoms. Most tumours were WHO grade IV (80.0%), with frontal lobe involvement being the predominant tumour location (56.7%). IDH mutation was detected in 90.0% of patients, and gross total resection was achieved in 76.7%.

Table 1: Baseline demographic, clinical, tumour, and treatment characteristics of the study population.

Characteristic	n (%) / Value
Age (years)	
Range	21-59
Mean ± SD	45.9 ± 10.9
Median (IQR)	49 (34.75-54.75)
Age group	
21-30	3 (10.0)
31-40	7 (23.3)
41-50	8 (26.7)
51-60	12 (40.0)
Gender	
Male	24 (80.0)
Female	6 (20.0)
Comorbidities	
None	25 (83.3)
Diabetes mellitus	3 (10.0)
Hypertension	2 (6.7)
Presenting symptoms	
Headache	15 (50.0)
Seizure	10 (33.3)
Hemiparesis	5 (16.7)
Memory impairment	2 (6.7)
Vomiting	2 (6.7)
Speech defect	1 (3.3)
Loss of power	1 (3.3)
Altered sensorium	1 (3.3)
WHO tumour grade	
Grade III	6 (20.0)
Grade IV	24 (80.0)
Tumour laterality	
Right	16 (53.3)
Left	14 (46.7)
Tumour location	
Frontal	17 (56.7)
Parietal	9 (30.0)
Occipital	2 (6.7)
Temporal	1 (3.3)
Frontoparietal	1 (3.3)
ECOG performance status	
ECOG 1	20 (66.7)
ECOG 2	10 (33.3)
IDH status	
Mutant	27 (90.0)
Wild type	3 (10.0)
Type of surgery	
Gross total resection	23 (76.7)
Tumour decompression	6 (20.0)
Excisional biopsy	1 (3.3)
Concurrent TMZ dose	

100 mg	8 (26.7)
120 mg	20 (66.7)
140 mg	2 (6.7)

Radiological response: Serial MRI demonstrated a progressive reduction in tumour size throughout follow-up [Table 2]. The proportion of lesions measuring <2 cm increased from 23.3% at baseline to 46.7% at 6 weeks and 73.3% at 3 months, with a corresponding decline in larger lesions. Overall, the reduction in tumour size compared with baseline was statistically significant ($p < 0.0001$).

Table 2: Distribution of tumour size on serial MRI assessment during follow-up.

Tumour size	Baseline	6 weeks	3 months
<2 cm	7 (23.3)	14 (46.7)	22 (73.3)
2–4 cm	17 (56.7)	14 (46.7)	8 (26.7)
>4 cm	6 (20.0)	2 (6.7)	0

Radiological response according to RECIST version 1.1 is presented in [Table 3]. At 6 weeks, stable disease was observed in 93.3% of patients, whereas pseudoprogression occurred in 6.7%. At 3 months, one patient (3.3%) achieved a near-complete response, six patients (20.0%) demonstrated a partial response, twenty-two patients (73.3%) maintained stable disease, and one patient (3.3%) showed disease progression.

Table 3. Radiological response according to RECIST version 1.1.

Response	6 weeks	3 months
Near complete response	0	1 (3.3)
Partial response	0	6 (20.0)
Stable disease	28 (93.3)	22 (73.3)
Progressive disease	0	1 (3.3)
Pseudoprogression	2 (6.7)	0

Haematological safety: Haematological parameters remained stable during treatment and follow-up [Table 4]. Mean haemoglobin, total leukocyte count, and platelet count remained within normal limits throughout the study period. Anaemia occurred in one patient during follow-up, while leukopenia was observed in one patient at each assessment. No cases of thrombocytopenia were reported [Table 5]. Liver function tests, renal function tests, and serum electrolyte levels remained within normal limits in all patients.

Table 4: Haematological parameters

Parameter	End of RT	1 month	3 months
Haemoglobin (g/dL)	12.72 ±1.59	12.47 ±1.34	12.63 ±1.44
Total leukocyte count ($\times 10^3/\mu L$)	6.33 ±1.74	6.63 ±1.43	7.04 ±1.58
Platelet count ($\times 10^5/\mu L$)	1.96 ±0.53	2.26 ±0.50	1.97 ±0.50

Table 5: Treatment-related haematological toxicities during follow-up.

Toxicity	End RT	1 month	3 months
Anaemia	0	1	0
Leukopenia	1	1	1
Thrombocytopenia	0	0	0
Grade 3–4 toxicity	0	0	0

No grade 3 or grade 4 haematological toxicities were observed, and no treatment interruptions, dose reductions, or treatment discontinuations were required. All patients completed the planned course of concurrent chemoradiotherapy.

Clinical Symptom Assessment: Neurological symptoms during follow-up are summarised in Table 6. Mild headache persisted in one patient throughout follow-up. No seizures occurred at treatment completion or at the 1-month assessment; however, one patient experienced a seizure at 3 months, corresponding with radiological disease progression. Subjective cognitive impairment was reported in one patient at 1 month and in two patients at 3 months. No patients developed altered sensorium or memory impairment during follow-up.

Table 6: Neurological symptoms during follow-up.

Symptom	End RT	1 month	3 months
Headache	1	1	1
Seizure	0	0	1
Cognitive impairment	0	1	2
Memory impairment	0	0	0
Altered sensorium	0	0	0

Discussion

High-grade gliomas remain among the most aggressive primary brain tumours, with poor survival despite advances in surgery, radiotherapy, and systemic therapy. In this prospective observational study, hypofractionated concurrent chemoradiotherapy using 58.5 Gy in 25 fractions with temozolomide demonstrated encouraging early radiological response, excellent treatment compliance, and minimal treatment-related toxicity. Most patients achieved radiological disease stability or tumour regression during the 3-month follow-up, and no grade 3-4 haematological toxicities, treatment interruptions, or dose modifications were observed. Overall, these favourable clinical and radiological outcomes and the low incidence of significant treatment-related toxicity were broadly consistent with previous studies of hypofractionated chemoradiotherapy and appeared comparable to or lower than those reported in the literature.[14-16] These findings suggest that moderately hypofractionated radiotherapy may provide encouraging short-term radiological outcomes while maintaining an acceptable safety profile in carefully selected patients with high-grade glioma.

CNS tumours account for approximately 2% of all malignancies in India, with high-grade gliomas representing an important proportion of malignant tumours encountered in neuro-oncology practice.[17,18] Although multimodal treatment has improved outcomes, prognosis remains poor, prompting continued efforts to optimise radiotherapy delivery while maintaining efficacy and minimising treatment-related toxicity. In resource-constrained healthcare systems, where limited radiotherapy infrastructure and long waiting lists are common, treatment schedules that reduce overall treatment time are particularly attractive.

The demographic and clinicopathological characteristics of our cohort were broadly consistent with the existing literature. The median age of 49 years was somewhat younger than that reported in large Western registries such as GLOBOCAN and the Central Brain Tumor Registry of the United States (CBTRUS), where the median age at diagnosis is generally in the mid-fifties.[1,19,20] Similar observations have been reported in several Indian and other South Asian studies, reflecting regional demographic differences and referral patterns. Male predominance was also observed, with males accounting for 80% of the study population. Although sex-related biological differences, including the potential protective role of oestrogen signalling, have been proposed, environmental exposures, occupational factors, and healthcare access may also contribute to this disparity.[21] Most patients had WHO grade IV tumours, good baseline performance status, and underwent maximal safe surgical resection before chemoradiotherapy, reflecting current clinical practice for high-grade gliomas.

The 2021 WHO Classification of Tumours of the CNS has substantially advanced glioma classification by integrating molecular alterations with histopathological findings.[3] The redefinition of glioblastoma as an IDH-wild-type diffuse astrocytic tumour with characteristic molecular features represents a major advance in neuro-oncology. In our cohort, IDH profiling contributed to the molecular characterisation of tumours and supported contemporary diagnostic classification. Although comprehensive molecular testing remains unavailable in many centres across low- and middle-income countries, broader implementation of biomarkers such as IDH mutation, 1p/19q codeletion, and MGMT promoter methylation remains important for prognostication, therapeutic selection, and enrolment into precision oncology trials.

The principal finding of this study was the favourable early radiological response observed following hypofractionated concurrent chemoradiotherapy. Serial MRI demonstrated a progressive reduction in tumour size, with the proportion of lesions measuring less than 2 cm increasing significantly during follow-up. At 3 months, the majority of patients exhibited either stable disease or objective tumour regression, while disease progression was observed in only one patient. These findings suggest that the present regimen provides encouraging early radiological outcomes in this selected cohort, consistent with the potential efficacy of hypofractionated approaches reported in the literature.[22]

The radiological findings were accompanied by a generally favourable clinical symptom profile. Neurological symptoms remained infrequent during follow-up, with headache, seizure recurrence, and cognitive impairment reported in only a small proportion of patients. However, these encouraging early findings should be interpreted cautiously because glioblastoma is characterised by diffuse infiltration beyond radiologically visible disease. Previous pathological and imaging studies have consistently demonstrated that 78-90% of recurrences occur within 2 cm of the original tumour bed despite aggressive multimodal treatment.[23,24] Consequently, early radiological response does not necessarily predict durable disease control, highlighting the continued importance of scheduled MRI surveillance following treatment.

The biological rationale for hypofractionated radiotherapy is supported by the linear-quadratic model, whereby increasing the dose per fraction enhances biological effectiveness while shortening overall treatment duration, thereby potentially reducing opportunities for accelerated tumour repopulation. In addition, shorter treatment schedules may decrease radiation-induced lymphopenia, which has emerged as an adverse prognostic factor in patients with glioblastoma.[25] Preservation of lymphocyte counts may also have increasing relevance with the growing interest in combining radiotherapy with immunotherapeutic approaches.

An important observation in our study was the excellent treatment tolerability. No grade 3 or grade 4 haematological toxicities were observed, and all patients completed the planned course of concurrent chemoradiotherapy without treatment interruption or dose reduction. Haemoglobin levels, leukocyte counts, platelet counts, liver function, renal function, and serum electrolyte levels remained stable throughout treatment and follow-up. Although late toxicities such as radionecrosis, neurocognitive decline, and endocrine dysfunction require longer observation, the favourable acute toxicity profile observed in our cohort supports the feasibility of this moderately hypofractionated regimen.

Current international guidelines from the European Society for Radiotherapy and Oncology (ESTRO) and the European

Association of Neuro-Oncology (EANO) recommend hypofractionated radiotherapy primarily for elderly patients or those with poor performance status. Various schedules, including 40.05 Gy in 15 fractions, 34 Gy in 10 fractions, and 25 Gy in five fractions, have demonstrated outcomes comparable with conventional fractionation in appropriately selected patients.[26] The phase II study by Navarria et al. further demonstrated that hypofractionated radiotherapy combined with temozolomide achieved survival outcomes comparable to conventional radiotherapy without increasing treatment discontinuation or severe radiation necrosis.[27] Our findings extend these observations by demonstrating encouraging early radiological response and excellent tolerability using a moderately hypofractionated 5-week schedule in a relatively younger cohort with good performance status.

The present regimen of 58.5 Gy delivered in 25 fractions was selected to provide a biologically effective dose comparable to conventional fractionation while reducing overall treatment duration by approximately one week. Shortening radiotherapy may offer several practical advantages, including fewer hospital visits, reduced travel-related expenses, lower caregiver burden, improved patient convenience, and more efficient utilisation of radiotherapy resources. These considerations are particularly relevant in India and other low- and middle-income countries, where limited radiotherapy infrastructure and prolonged waiting times may delay treatment initiation. A shorter treatment schedule may therefore improve the feasibility of timely treatment delivery in appropriately selected patients.

The strengths of this study include its prospective design, uniform treatment protocol, systematic assessment of radiological response and treatment-related toxicities, and evaluation of a moderately hypofractionated regimen in a relatively younger population with good performance status. These features provide useful preliminary evidence regarding the feasibility of hypofractionated concurrent chemoradiotherapy in routine clinical practice.

This study also has several limitations. The sample size was relatively small, the study was conducted at a single institution, and follow-up was limited to three months, precluding evaluation of long-term endpoints such as progression-free survival, overall survival, late radiation-induced toxicity, and neurocognitive outcomes. In addition, quality-of-life assessments were not performed. Larger multicentre prospective studies with longer follow-up and appropriate comparative groups are therefore required to validate these findings and establish the long-term efficacy and safety of this treatment approach.

Conclusion

In summary, hypofractionated concurrent chemoradiotherapy delivering 58.5 Gy in 25 fractions with temozolomide demonstrated encouraging early radiological response, excellent treatment compliance, and minimal acute toxicity in patients with high-grade glioma. Although longer follow-up and comparative randomised studies are required before widespread adoption, this regimen appears to be a practical and clinically feasible alternative that may be particularly valuable in resource-limited settings where optimising radiotherapy capacity is an important consideration.

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Conflicts of interest

There are no conflicts of interest.

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