Original Article

Functional Preservation and Oncologic Outcomes with Hypofractionated Chemoradiotherapy in Elderly Glioblastoma: A Prospective Cohort Study

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Abstract

Background: Elderly patients with glioblastoma (GBM) have limited options due to frailty, comorbidities, and poor tolerance to standard chemoradiation. Hypofractionated radiotherapy (HFRT) offers a shorter, feasible alternative, but prospective data on functional preservation are scarce. **Material and Methods:** This prospective cohort (2019–2021) included 25 patients aged ≥60 years with histologically confirmed GBM. All underwent maximal safe resection followed by HFRT (40.05 Gy/15 fractions); adjuvant temozolomide (TMZ) was delivered when feasible. Primary endpoints were functional preservation [Karnofsky Performance Status (KPS), motor power, cognition, bowel/bladder function] and treatment-time efficiency. Secondary endpoints were progression-free survival (PFS), overall survival (OS), and landmark survival rates. **Results:** Median age was 63.7 years; 84% had gross total resection (GTR). Treatment adherence was high: 96% completed RT in a mean 21 days, with 76% managed entirely as outpatients and only 24% requiring short hospitalizations (mean 4.5 days). At 12 weeks, functional preservation efficiency (FPE) was 80%, motor improved in 44%, and mild cognitive decline occurred in 20%. Radiologic control (CR/SD) was seen in 32%. Median PFS was 5.7 months (PFS-6: 48%), and median OS was 8.0 months (OS-6: 68%; OS-12: 16%). GTR significantly improved PFS (5.9 vs. 4.6 months, p = 0.028) and PFS-6 (57% vs. 0%). Adjuvant TMZ yielded higher OS-6 (74% vs. 50%) and OS-12 (21% vs. 0%), though not statistically significant. **Conclusion:** HFRT with TMZ is feasible, function-preserving, and efficient in elderly GBM, minimizing hospitalization burden. Extent of resection remains the strongest determinant of disease control, underscoring the role of maximal cytoreduction even in frail patients.

Keywords: Glioblastoma; Hypofractionated radiotherapy; Temozolomide; Functional preservation

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Introduction

Glioblastoma (GBM) is the most common and aggressive primary brain tumor in adults, accounting for nearly half of all malignant gliomas, with an annual incidence of 3–4 per 100,000 population.[1,2] Prognosis remains dismal, with median overall survival (OS) rarely exceeding 15 months despite multimodality therapy.[3] Outcomes are particularly poor in elderly patients (≥65 years), who present with higher rates of comorbidities, frailty, and treatment-related toxicities.[4,5]

Maximal safe surgical resection followed by radiotherapy (60 Gy in 30 fractions) with concomitant and adjuvant temozolomide (TMZ) is established as the standard of care in younger, fit patients.[6] However, the applicability of this regimen in elderly cohorts is limited by risks of neurocognitive decline, logistical burden, and reduced quality of life.[7,8] Evidence suggests that long-course RT may accelerate cognitive impairment through hippocampal and white matter injury, making shorter regimens attractive in vulnerable populations.[9]

Hypofractionated radiotherapy (HFRT), most commonly 40 Gy in 15 fractions, has emerged as a pragmatic alternative. Multiple randomized trials demonstrate non-inferior survival and acceptable toxicity compared with conventional schedules.[10,11] The pivotal NCIC-EORTC CE.6 trial confirmed that HFRT with TMZ significantly improved OS and progression-free survival (PFS) while preserving quality of life in patients ≥65 years.[12] Other trials, including the Nordic study, further support HFRT as superior to standard RT or TMZ alone in selected subgroups.[13]

Despite these advances, there remains a paucity of prospective data on functional preservation—particularly maintenance of performance status, cognition, motor function, and independence—in elderly patients treated with HFRT ± TMZ. The real-world impact on hospitalization requirements and outpatient feasibility is also underexplored. In addition, extent of resection remains a powerful prognostic factor across all age

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groups, with gross total resection (GTR) consistently conferring superior outcomes.[14,15]

This prospective cohort study was designed to evaluate functional preservation, treatment-time efficiency, and oncologic outcomes in elderly GBM patients treated with HFRT with or without TMZ.

Materials and Methods

Study Design and Patient Selection

This was a prospective single-institution cohort study conducted in the Department of Radiation Oncology between May 2019 and September 2021.

Inclusion criteria were:

1. Age ≥ 60 years.
2. Histopathological confirmation of GBM
3. Postoperative Karnofsky Performance Status (KPS) ≥ 50.
4. Adequate baseline cognitive function [Mini-Mental State Examination (MMSE) ≥ 24].
5. Ability to provide informed consent and comply with planned treatment and follow-up schedules.

Exclusion criteria included:

Prior cranial radiotherapy, history of other active malignancies, uncontrolled systemic illness, severe psychiatric or cognitive impairment precluding assessment, or patient refusal.

A total of 25 patients meeting eligibility criteria were prospectively enrolled. Institutional Ethics Committee approval was obtained prior to study initiation, and all patients provided written informed consent.

Surgical Management: All patients underwent neurosurgical resection with intent for maximal safe debulking. Extent of resection was categorized as gross total resection (GTR) or subtotal resection (STR) based on postoperative MRI within 72 hours.

Radiotherapy Protocol: Adjuvant radiotherapy was initiated within 6 weeks of surgery. Patients were immobilized in supine position with a thermoplastic head mask. Planning CT scans (2–3 mm slices) were acquired and co-registered with postoperative MRI for target delineation.

- **Target volumes:**
  - Gross Tumor Volume (GTV): surgical cavity and any residual enhancing tumor.
  - Clinical Target Volume (CTV): GTV with a uniform 2-cm margin, modified for anatomical barriers.
  - Planning Target Volume (PTV): CTV with 3–5 mm isotropic expansion.
- **Radiotherapy schedule:** 40.05 Gy in 15 daily fractions (2.67 Gy/fraction) over 3 weeks, delivered by conformal radiotherapy techniques (3D-CRT or IMRT) on linear accelerators.
- **Treatment verification:** Daily patient positioning was verified with on-board imaging, and portal dosimetry was performed weekly.

Chemotherapy Protocol: Adjuvant chemotherapy with temozolomide (TMZ) was recommended for all patients unless contraindicated due to comorbidities or intolerance.

- **Concurrent phase:** TMZ at 75 mg/m² orally once daily throughout the RT course.
- **Adjuvant phase:** Following RT, TMZ was administered at 150–200 mg/m²/day orally for 5 days every 28 days, up to 6 cycles, depending on tolerance and hematologic profile.

Clinical and Neurologic Assessment: Baseline evaluation included detailed neurological examination, KPS, MMSE, and bowel/bladder function assessment.

- **On-treatment evaluation:** Weekly during RT for acute toxicity, steroid requirement, seizures, and compliance.
- **Post-treatment follow-up:** At 6 weeks post-RT and then every 2 months until progression.

Neurologic outcomes were classified as improved, stable, or worsened based on motor power, MMSE, and KPS. Functional Preservation Efficiency (FPE) was defined as the proportion of patients with improved or stable KPS at 12 weeks.

Radiologic Evaluation: Magnetic resonance imaging (MRI) with contrast was performed at 12 weeks post-RT, and subsequently every 2–3 months or as clinically indicated. Disease status was assessed according to RANO criteria, categorized as complete response (CR), stable disease (SD), or progressive disease (PD).

Toxicity Assessment: Acute toxicities were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Neurocognitive impairment was defined as MMSE < 24 at follow-up. Hematologic parameters were monitored before each chemotherapy cycle.

Endpoints

- **Primary endpoints:**
  - Functional preservation (KPS, MMSE, motor function, bowel/bladder status at 12 weeks).
- **Secondary endpoints:**
  - Progression-free survival (PFS): time from surgery to radiologic/clinical progression or death.
  - Treatment-time efficiency (overall treatment time, hospitalization burden).
  - Overall survival (OS): time from surgery to death from any cause.
  - Landmark survival rates (PFS-6, OS-6, OS-12).
  - Influence of extent of resection and adjuvant TMZ on outcomes.

Statistical Analysis: All analyses were performed using IBM SPSS software version 25. Descriptive statistics summarized baseline characteristics and treatment compliance. Kaplan–Meier method estimated OS and PFS; differences between subgroups were compared using the log-rank test. Categorical variables (neurologic outcomes, functional preservation, hospitalization) were compared using chi-square or Fisher's exact test. p-values < 0.05 were considered statistically significant.

Results

Patient Characteristics: Between May 2019 and September 2021, a total of 25 elderly patients (≥60 years) with histologically confirmed glioblastoma multiforme (GBM) were prospectively enrolled. The study population comprised 15 males (60%) and 10 females (40%), with a mean age of 63.7 ± 3.2 years (range, 61–72). A majority of patients (72%) were between 61 and 65 years of age, while 20% were aged 66–70, and only two patients (8%) were above 70 years.

The parietal lobe was the most frequently affected site (32%), followed by multilobe involvement (28%), frontal lobe (24%), and temporal lobe (16%). Gross total resection (GTR) was achieved in 21 patients (84%), whereas 4 patients (16%) underwent subtotal resection (STR). Postoperative MRI confirmed residual disease in 16% of the cohort.

At baseline, performance status was moderately impaired in most patients: 20 (80%) had KPS 60–70, and 5 (20%) had KPS <60, with a mean KPS of 59.6 ± 6.1. Despite this, cognitive function was preserved across the cohort, with all patients scoring ≥24 on MMSE. Bowel and bladder function was intact in 20 patients (80%), while 5 (20%) had deficits prior to treatment.

Baseline demographic and clinical characteristics are presented in [Table 1].

Treatment Delivery and Efficiency: All patients commenced radiotherapy within 6 weeks of surgery. Hypofractionated radiotherapy (40.05 Gy in 15 fractions over 3 weeks) was delivered in all cases, with a mean overall treatment time (OTT) of 21.3 ± 1.4 days. Treatment compliance was high: 24 patients (96%) completed the planned RT, while only one patient discontinued prematurely after 10 fractions due to clinical deterioration.

Nineteen patients (76%) received adjuvant temozolomide (TMZ). The remaining 6 patients (24%) did not receive chemotherapy due to comorbidities or loss to follow-up.

Hospitalization during RT was required in 6 patients (24%), with a mean inpatient stay of 4.5 ± 1.0 days. Admissions were primarily for seizure management, steroid-related complications, or exacerbation of comorbidities. Importantly, 76% of patients completed RT entirely on an outpatient basis, indicating the feasibility and convenience of the short-course regimen in elderly patients with limited functional reserve. Furthermore, no additional unplanned hospitalizations occurred in the first month post-RT, underscoring the tolerability of this approach.

Table 1: Baseline Clinical and Tumor Characteristics of the Study Population

Characteristic	Category	n (%)
Age Group (years)	61–65	18 (72%)
	66–70	5 (20%)
	71–75	2 (8%)
Mean Age		63.72 ± 3.16
Gender	Male	15 (60%)
	Female	10 (40%)
Site of Lesion	Frontal	6 (24%)
	Parietal	8 (32%)
	Temporal	4 (16%)
	Multilobe	7 (28%)
Type of Resection	Gross Total Resection	21 (84%)
	Subtotal Resection	4 (16%)
Postoperative Imaging	Residual Disease Present	4 (16%)
	Only Postoperative Changes	21 (84%)
Baseline KPS Score	< 60	5 (20%)
	60–70	20 (80%)
Mean KPS Score		59.6 ± 6.11
Cognition (MMSE)	No Impairment	25 (100%)
Bowel/Bladder Function	Intact	20 (80%)
	Affected	5 (20%)

Acute Events and Treatment Tolerability

Treatment was well tolerated overall. Seizures occurred in 2 patients (8%) despite prophylactic antiepileptics. Corticosteroid dose escalation was required in 8 patients (32%), largely for edema-related symptoms. Hematologic toxicities were absent, and no grade ≥3 adverse events were observed. Non-hematologic toxicities were limited to mild fatigue, nausea, and transient cognitive changes.

Functional and Neurologic Outcomes

At 12 weeks post-RT, functional and neurologic assessments demonstrated encouraging results.

- KPS: Nine patients (36%) improved, 11 (44%) remained stable, and 5 (20%) declined, corresponding to a Functional Preservation Efficiency (FPE) of 80%.
- Motor power: Improvement was documented in 11 patients (44%), stability in 9 (36%), and deterioration in 5 (20%).
- Cognition: Mild MMSE decline (scores 18–23) occurred in 5 patients (20%), while the majority retained intact cognitive function.
- Bowel/bladder function: Stable in 88% of patients, with new or worsened deficits in 12%.

When motor power and KPS were analyzed together, 72% of patients exhibited concordant improvement or stability in both domains, highlighting consistency between performance status and neurologic outcomes.

Table 2: Functional and neurologic outcomes at 12 weeks post-RT

Outcome measure	Improved n (%)	Stable n (%)	Declined n (%)	FPE* (%)
Karnofsky Performance Status (KPS)	9 (36)	11 (44)	5 (20)	80
Motor power	11 (44)	9 (36)	5 (20)	—
Mini-Mental State Examination (MMSE)†	—	20 (80)	5 (20)	—
Bowel/bladder function	0 (0)	22 (88)	3 (12)	—

Radiologic Response

MRI at approximately 12 weeks post-RT revealed:

- Complete response (no residual or recurrent disease): 3 patients (12%)
- Stable residual disease: 5 patients (20%)
- Progressive disease/recurrence: 16 patients (64%)

Progression was observed predominantly in patients who had undergone subtotal resection, reaffirming the importance of maximal surgical debulking in disease control. No partial responses were documented, which likely reflects the persistence of post-surgical enhancement in most patients.

Survival Outcomes

At a median follow-up of 4.9 months (mean 4.8 ± 1.5), 6 patients (24%) remained alive, while 19 (76%) had died, including one during RT.

- Progression-Free Survival (PFS): The median PFS for the cohort was 5.69 months. The 6-month PFS (PFS-6) rate was 48%. Patients undergoing GTR achieved significantly superior outcomes, with median PFS 5.89 vs. 4.61 months for STR (p = 0.028) and a PFS-6 rate of 57% vs. 0%. Furthermore, 15% of GTR patients remained progression-free at 12 months, while none of the STR subgroup achieved this milestone. Use of adjuvant TMZ improved PFS-6 (53% vs. 33%), though differences did not reach statistical significance. Baseline KPS ≥60 also favoured PFS-6 (50% vs. 40% for KPS <60), but without statistical significance.
- Overall Survival (OS): Median OS was 7.99 months. The OS-6 and OS-12 rates were 68% and 16%, respectively. Patients undergoing GTR demonstrated numerically better survival than STR (median OS 7.99 vs. 4.87 months; OS-6: 71% vs. 50%, p = 0.092; OS-12: 19% vs. 0%). Adjuvant TMZ was associated with improved OS (OS-6: 74% vs. 50%; OS-12: 21% vs. 0%), although these did not reach statistical significance. Patients with baseline KPS ≥60 also had modestly improved survival (OS-6: 70% vs. 60%; OS-12: 18% vs. 0%).

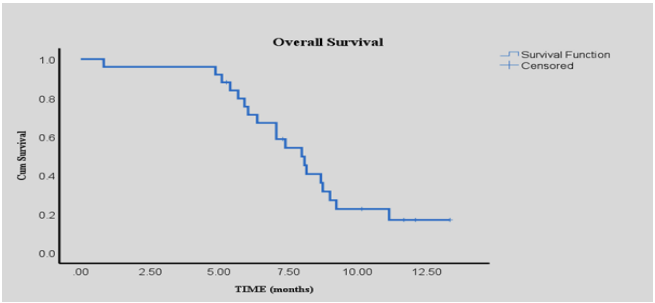

Figure 1: Kaplan–Meier Curve for Overall Survival of Study Cohort.

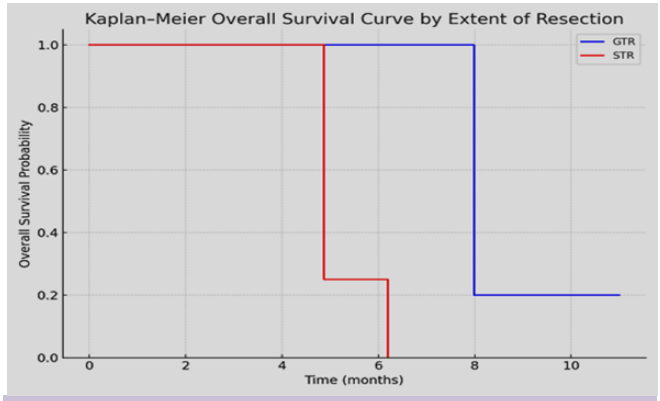

Figure 2: Comparison of overall survival between patients who underwent gross total resection (GTR) and those who underwent subtotal resection (STR).

Key Determinant of Disease Control

Across all analyses, the extent of resection emerged as the most consistent determinant of disease control. Patients undergoing GTR achieved superior PFS, higher PFS-6 rates, and a measurable likelihood of being progression-free at 12 months, compared with uniformly poor outcomes in STR patients. While OS differences did not reach statistical significance, GTR consistently conferred a numerical survival advantage. These findings reinforce that, even in elderly GBM treated with short-course chemoradiation, maximal safe resection translates into more durable disease control and improved functional preservation.

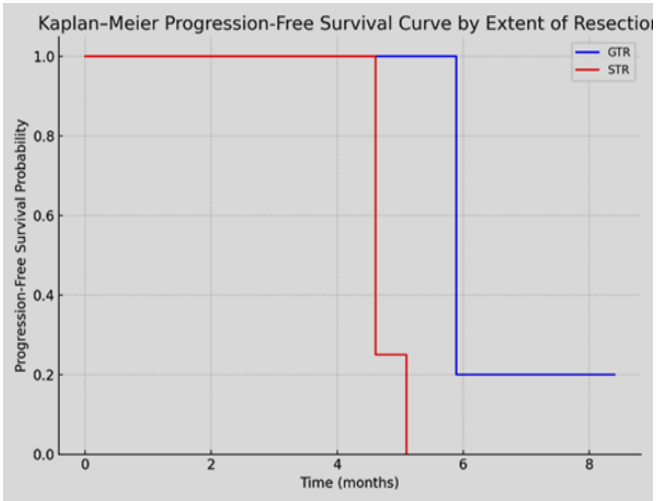

Figure 3: Comparison of Progression free survival between patients who underwent gross total resection (GTR) and those who underwent subtotal resection (STR).

Table 3: Landmark survival outcomes (PFS-6, OS-6, OS-12) by key subgroups

Subgroup	n	PFS-6 (%)	p-value	OS-6 (%)	p-value	OS-12 (%)	p-value
Overall cohort	25	48	—	68	—	16	—
Extent of resection							
GTR	21	57	0.028	71	0.092	19	0.15
STR	4	0		50		0	
Adjuvant TMZ							
Yes	19	53	0.21	74	0.18	21	0.12
No	6	33		50		0	

Baseline KPS							
≥ 60	20	50	0.65	70	0.64	18	0.62
< 60	5	40		60		0	

Landmark survival outcomes by subgroup are presented in [Table 3].

Discussion

Glioblastoma in the elderly remains a major therapeutic challenge, with survival consistently worse than in younger populations due to frailty, comorbidities, and reduced treatment tolerance.[1,4,5] While the Stupp regimen established combined RT and TMZ as the standard of care in younger adults,[6] it excluded most patients over 70 years, leaving uncertainty about optimal strategies for the elderly. Our study contributes prospective evidence on the feasibility of HFRT with or without TMZ in this population, emphasizing patient-centred outcomes.

Functional preservation and neurologic outcomes

In elderly GBM, maintaining independence and neurologic function may be more meaningful than marginal gains in survival. In our study, 80% achieved functional preservation efficiency at 12 weeks, consistent with Minniti et al., who showed that HFRT + TMZ stabilizes neurocognition and quality of life.[16] Similarly, Keime-Guibert et al. demonstrated that radiotherapy, even in elderly patients with poor performance status, improved functional independence compared with supportive care alone.[17] More recently, Zhu et al. confirmed that hypofractionated regimens preserve health-related quality of life without added neurotoxicity.[18] These findings highlight the importance of incorporating functional outcomes into routine reporting, not just survival metrics.

Treatment-time efficiency and feasibility

Shortened regimens are especially relevant when remaining life expectancy is limited. Our findings of high treatment compliance, minimal hospitalization, and predominantly outpatient completion mirror those of Roa et al., who first demonstrated the non-inferiority of 40 Gy/15 fractions versus 60 Gy/30 in patients ≥60 years.[10] Later, the IAEA trial validated even shorter schedules such as 25 Gy in 5 fractions, again showing comparable outcomes.[11] Meta-analyses now confirm that hypofractionated regimens reduce treatment burden without compromising efficacy.[18,19] In resource-constrained settings, this approach is particularly valuable, allowing treatment completion with minimal disruption to patients' autonomy.

Role of temozolomide

The CE.6 trial (Perry et al.) remains practice-changing, establishing that HFRT combined with TMZ significantly improves OS (9.3 vs. 7.6 months) and PFS, especially in MGMT-methylated patients.[12] Our results echo these findings, with patients receiving TMZ achieving numerically better OS-6 and OS-12 rates. Although not statistically significant in our small cohort, the trend supports TMZ integration where feasible, consistent with EANO and NCCN guideline recommendations.[20,21]

Extent of resection as a determinant of control

The impact of cytoreduction was reaffirmed in our study, with GTR significantly improving PFS and conferring a numerical OS benefit. This aligns with large retrospective analyses showing that extent of resection is among the strongest predictors of survival in GBM, including elderly patients.[14,15,22] Sanai and Berger's surgical series established that greater resection extent correlates with longer survival, even when adjusted for age.[23] Thus, maximal safe resection should remain a cornerstone, followed by individualized adjuvant therapy.

Survival outcomes in context

Our median OS (7.9 months) and PFS (5.7 months) are comparable with prior prospective studies. The Nordic trial confirmed that HFRT is equivalent or superior to standard RT, and better than TMZ alone in MGMT-unmethylated tumors.[13] These consistent results reinforce HFRT ± TMZ as the pragmatic standard of care for elderly GBM.

Strengths and limitations: The strengths of our study include its prospective design, systematic evaluation of functional outcomes, and real-world assessment of hospitalization burden—domains often underreported in elderly GBM research. Limitations include the modest sample size and lack of molecular stratification (MGMT, IDH), which could refine prognostic interpretation. Future work should integrate biomarker status with patient-centred endpoints.

Clinical implications: Our data, in line with international evidence, suggest that HFRT with TMZ provides a practical balance between efficacy, functional preservation, and treatment efficiency. Moreover, the extent of resection remains the strongest determinant of disease control. These results support HFRT as a preferred approach for elderly GBM in both high-resource and resource-limited settings.

Conclusion

Hypofractionated radiotherapy with temozolomide is a feasible and well-tolerated option for elderly glioblastoma patients, offering meaningful functional preservation and reduced treatment burden. Extent of surgical resection remains the most critical determinant of disease control, underscoring the value of maximal safe cytoreduction in this population.

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Conflicts of interest

There are no conflicts of interest.

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