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PRECISION THROUGH MODERATION: REDEFINING GBM THERAPY IN THE ELDERLY WITH HYPOFRACTIONATED RADIOTHERAPY

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ABSTRACT

Background: Glioblastoma (GBM) is the most aggressive primary brain tumor, with particularly poor prognosis in elderly patients due to age-related comorbidities and reduced treatment tolerance. Standard therapy based on the Stupp protocol is often poorly suited to this population. Hypofractionated radiotherapy (HFRT) has emerged as a promising alternative, but optimal regimens and outcomes remain under investigation. **Methods:** This prospective single-arm study included 25 patients aged ≥60 years with histologically confirmed GBM and Karnofsky Performance Status (KPS) >50. All patients underwent maximal safe resection followed by HFRT (40.05 Gy in 15 fractions) with concurrent temozolomide (TMZ) and adjuvant TMZ per the Stupp protocol. The primary endpoint was overall survival (OS); secondary endpoints included progression-free survival (PFS), treatment compliance, toxicity, and neurologic outcomes. **Results:** The median age was 63.7 years. Gross total resection was achieved in 84% of patients. Adjuvant TMZ was administered in 76%. Median OS and PFS were 7.99 and 5.69 months, respectively. Extent of resection significantly influenced PFS ($p = 0.028$), but not OS. Treatment was well tolerated, with no grade 3–4 hematologic toxicity. Post-treatment neurologic improvement was noted in 44% of patients, with stable or improved KPS in 80%. Mild cognitive decline occurred in 20% of patients. **Conclusion:** HFRT combined with TMZ is a feasible, effective, and well-tolerated treatment option for elderly GBM patients. It provides survival outcomes comparable to conventional regimens with improved tolerability and functional preservation. These findings support HFRT as a standard approach in appropriately selected elderly or frail patients.

INTRODUCTION:

Glioblastoma (GBM) is a highly aggressive and infiltrative brain tumor, characterized by poor survival outcomes, particularly in older adults. While the median overall survival is approximately 6.1 months, it declines further to around 3.2 months in patients over the age of 70 [1]. The landmark Stupp protocol helped standardize GBM treatment; however, patients older than 70 were excluded from this trial, and subsequent subgroup analyses have shown diminishing benefits of treatment with increasing age [2,3].

Elderly GBM patients frequently receive less intensive therapy due to concerns about increased toxicity, reduced potential benefit, and the presence of comorbid conditions [4–9]. Additionally, a significant proportion may opt out of aggressive treatment altogether [8]. As a result, there is no universally accepted treatment protocol for this population, and current practices vary widely— from best supportive care to comprehensive chemoradiotherapy [4,7,9]. Given that the median age at diagnosis is 64 years and the elderly population is steadily increasing, it is essential to develop individualized, age-appropriate treatment strategies [10]. However, a lack of consensus regarding the definition of "elderly"—with age thresholds ranging from 60 to 75 years—continues to challenge research and clinical decision-making [6]. Optimizing treatment in this demographic requires a delicate balance between extending survival and maintaining functional independence. Age remains one of the most significant negative prognostic indicators.

Similarly, performance status—particularly a Karnofsky Performance Score (KPS) above 70—is a critical factor in determining eligibility for aggressive treatment modalities [7]. Nevertheless, KPS may not always reflect true physiological reserve, as neurological impairments caused by the tumor itself can lower the score without indicating overall frailty [5].

The current standard of care for GBM includes maximal safe surgical resection, followed by concurrent radiotherapy and temozolomide (TMZ), and subsequent adjuvant TMZ. Despite this aggressive multimodality approach, survival outcomes in elderly patients remain dismal. In light of these challenges, we designed a prospective single-arm study to evaluate the role of hypofractionated radiotherapy in elderly GBM patients, focusing on overall survival and treatment-related toxicities.

MATERIAL AND METHODS:

Participants:

This prospective study was conducted between January 2020 and January 2022. Patients aged over 60 years with histologically confirmed glioblastoma multiforme (GBM) and a Karnofsky Performance Status (KPS) >50 were included. Exclusion criteria were prior cranial radiotherapy, other active or prior invasive malignancies, inability to initiate radiotherapy within six weeks of surgery, and non-adherence to follow-up protocols. Patients without available pre- and postoperative imaging were also excluded. Institutional review board approval and written informed consent were obtained from all participants.

Study Design:

All enrolled patients underwent a thorough clinical, neurological, and laboratory evaluation, including CBC, liver and renal function tests. A central pathological review confirmed GBM diagnosis. Pre-radiotherapy imaging included contrast-enhanced brain MRI to assess surgical resection status.

Radiotherapy Protocol:

Radiotherapy was delivered via 3D-conformal radiotherapy (3D-CRT) using thermoplastic immobilization. CT simulation was done with a Philips wide-bore CT (3 mm slice thickness) using contrast (1 ml/kg). Treatment planning consisted of two clinical target volumes (CTV):

- **CTV32.04:** tumor with surrounding edema with 1.5–2 cm margin
- **CTV40.05:** T1-enhancing tumor with 1.5 cm marginA 5 mm isotropic margin was added to create planning target volumes (PTVs). A total dose of 40.05 Gy was delivered in 15 fractions (2.67 Gy/fraction) over three weeks using an Elekta Synergy linear accelerator. Image guidance with kilovoltage CBCT was performed on alternate days.

Chemotherapy:

Concurrent temozolomide (TMZ) was administered at 75 mg/m² daily from day 1 to 20 of radiotherapy. Adjuvant TMZ followed the Stupp regimen: 150 mg/m² for cycle 1 and 200 mg/m² for up to five subsequent cycles every four weeks. Dose adjustments were made based on hematologic and non-hematologic toxicities. TMZ was discontinued if the dose dropped below 100 mg/m² or if grade 4 toxicities occurred. Supportive care, including steroids and antiemetics, was provided as required.

Toxicity And Follow-Up:

Weekly complete blood counts were performed during chemoradiotherapy and prior to each adjuvant cycle. Toxicity was graded using CTCAE v5.0 (2017). Follow-up brain MRIs were performed every 3 months post-treatment or earlier if clinically indicated. Response assessment followed RANO criteria.

Statistical Analysis:

The primary endpoint was overall survival (OS); secondary endpoints included progression-free survival (PFS), treatment compliance, and toxicity. OS was calculated from diagnosis to death; PFS from diagnosis to radiological progression. Data were analysed using STATA v12. Kaplan–Meier estimates were used for survival analysis, with univariate comparisons via the log-rank test. Cox proportional hazards regression was applied for multivariate analysis. Prognostic variables analysed included age, gender, seizure at presentation, type of surgery, AED use, IDH-1 and p53 mutations, MIB-1 labelling index, and radiation fractionation. A p-value <0.05 was considered statistically significant.

RESULTS:

Patient Demographics And Clinical Characteristics:

A total of 25 elderly patients (≥60 years) with histologically confirmed glioblastoma multiforme (GBM) were prospectively enrolled between May 2019 and September 2021. The cohort consisted of 15 males (60%) and 10 females (40%), with a mean age of 63.72 ± 3.16 years (range: 61–72). Most patients (72%) were in the 61–65 age group. The most frequently involved tumor site was the parietal lobe (32%), followed by multilobe (28%), frontal (24%), and temporal regions (16%). Gross total resection (GTR) was achieved in 21 patients (84%), while 4 patients (16%) underwent subtotal resection (STR). Postoperative imaging confirmed residual disease in 4 cases (16%). At baseline, 80% of patients had a Karnofsky Performance Status (KPS) between 60and 70, with a mean score of 59.6 ± 6.11. All patients had intact cognitive function, with MMSE scores ≥24. Bowel and bladder function was intact in 80% prior to treatment.

Table 1. 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 ±
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%)

Treatment Delivery And Tolerability:

All patients received hypofractionated radiotherapy to a total dose of 40.05 Gy in 15 fractions. The mean overall treatment time (OTT) was 21.28 ± 1.44 days. Six patients completed treatment within 3 weeks, 18 within 25 days, while one patient discontinued therapy after 10 fractions.

Adjuvant temozolomide (TMZ) was administered to 19 patients (76%), while 6 patients (24%) did not receive chemotherapy due to comorbidities or loss to follow-up. Two patients (8%) experienced seizures during radiotherapy, despite prophylactic antiepileptic use. Steroid dose escalation was required in 8 patients (32%), and 6 patients (24%) were hospitalized during treatment (mean stay: 4.5 ± 1.05 days).

Overall, treatment was well tolerated. No hematologic toxicity was observed. Mild cognitive decline (MMSE 18–23) was noted in 5 patients (20%) post-radiotherapy. Three patients (12%) reported deterioration in bowel or bladder function. In terms of neurological outcomes, 11 patients (44%) experienced improvement in motor power post-radiotherapy, 5 patients (20%) had deterioration, and 9 (36%) remained stable. KPS improved in 36% of patients, declined in 20%, and remained unchanged in 44%.

Follow-Up and Disease Status:

The median follow-up duration was 4.9 months (mean: 4.8 ± 1.5). At the time of analysis, 6 patients (24%) were alive, and 19

(76%) had died, including one during radiotherapy. Follow-up MRI at 3 months post-treatment revealed no residual or recurrent disease in 3 patients (12%), stable residual disease in 5 (20%), and recurrence in 16 (64%).

Survival Outcomes:

Overall Survival (OS)

The median overall survival for the cohort was 7.99 months.

Age-based analysis revealed no statistically significant difference:

- Age 66–70: 9.24 months
- Age 61–65: 7.4 months
- Age 71–75: 6.05 months (p = 0.515)

Similarly, no significant difference in OS was noted based on baseline KPS:

- KPS <60: 8.16 months
- KPS ≥60: 7.99 months (p = 0.543)

Patients who underwent GTR had a longer OS (7.99 months) compared to STR (4.87 months), although this did not reach statistical significance (p = 0.092).

Kaplan–Meier Survival Analysis:

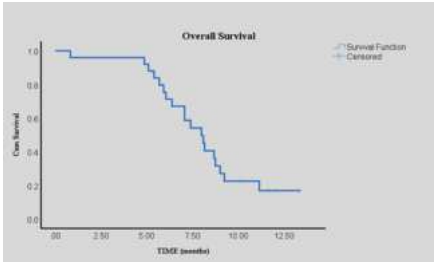

Figure 1. Kaplan–Meier Curve for Overall Survival of Study Cohort.

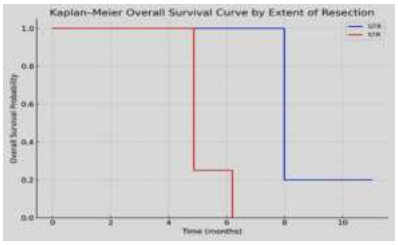

Figure 2. Comparison of overall survival between patients who underwent gross total resection (GTR) and those who underwent subtotal resection (STR).

Progression-Free Survival (PFS):

The median PFS for the cohort was 5.69 months. Stratified subgroup analysis showed:

- Age 66–70: 7.8 months
- Age 61–65: 5.1 months
- Age 71–75: 4.94 months (p = 0.783)

KPS had no significant influence on PFS:

- KPS ≥60: 5.69 months
- KPS <60: 5.13 months (p = 0.648)However, extent of surgical resection significantly influenced PFS:
- GTR: 5.89 months
- STR: 4.61 months (p = 0.028)

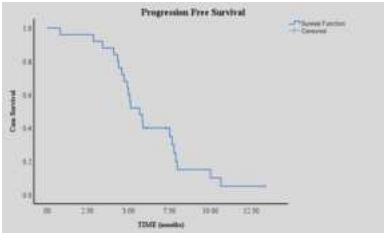

Figure 3. Kaplan–Meier Curve for Progression free Survival of Study Cohort.

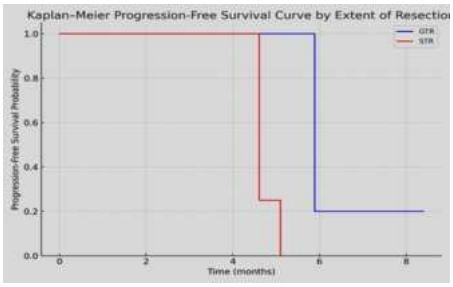

Figure 4. Comparison of Progression free survival between patients who underwent gross total resection (GTR) and those who underwent subtotal resection (STR).

At 1 year, 15% of patients with GTR remained progression-free, while none with STR were progression-free at 12 months. Kaplan–Meier curves for OS and PFS stratified by surgical extent are presented in Figures 1 and 2, respectively.

DISCUSSION:

Glioblastoma multiforme (GBM) is an aggressive brain tumor with poor survival outcomes, especially among the elderly. With a median age of diagnosis around 64 years and nearly half of patients over 65, optimizing treatment for this demographic is crucial. The Stupp protocol— maximal safe resection followed by normofractionated radiotherapy (RT) with concurrent and adjuvant temozolomide (TMZ)—is the established standard. However, it was validated primarily in patients under 70, with diminishing efficacy noted in older age groups.

Elderly patients face unique treatment barriers: limited physiologic reserve, comorbidities, cognitive concerns, and often distinct tumor biology. Genetic alterations such as TP53 and CDKN2A/p16 and overexpression of VEGF-A are more prevalent, often correlating with poorer prognosis. The MGMT promoter methylation status remains a key biomarker, with methylated patients deriving greater benefit from TMZ.

Hypofractionated radiotherapy (HFRT) has gained traction as an alternative to standard RT in this group, offering shorter treatment duration and potentially reduced toxicity. Advances like intensity-modulated radiotherapy (IMRT) and image guidance have improved precision, enabling the safe delivery of higher doses.

Several trials support HFRT. The Nordic trial showed that both HFRT and TMZ alone improved survival versus standard RT in patients ≥60. Roa et al.'s landmark phase III trial confirmed that 25 Gy in 5 fractions was non-inferior to 40 Gy in 15 fractions, with similar overall survival (OS), progression-free survival (PFS), and quality of life (QoL). In our study, using 40.05 Gy in 15 fractions plus TMZ, we observed a median OS of 7.99 months and PFS of 5.69 months— comparable to Roa's findings—affirming the effectiveness of this regimen.

The Perry et al. trial further supported the combination of TMZ with 40 Gy in 15 fractions in patients ≥65, demonstrating improved outcomes particularly in those with MGMT methylation. Our study showed that concurrent and adjuvant TMZ was well-tolerated and offered clinical benefit, with no grade 3–4 hematologic toxicity.

Extent of surgical resection significantly influenced PFS in our cohort, though not OS. This finding is in line with previous literature suggesting maximal resection contributes to better disease control. Furthermore, functional outcomes such as improved KPS and motor power post- treatment highlight the broader benefits of the hypofractionated approach.

Although some studies advocate dose escalation (e.g., 52.5

Gy in 15 fractions) for fit elderly patients, our findings support the feasibility and efficacy of the 40 Gy regimen for a wider population. It balances efficacy with patient convenience, especially in resource-constrained settings or when compliance is a concern.Preservation of quality of life is critical in elderly GBM management. Although formal QoL tools were not employed in our study, indicators such as MMSE, neurologic function, and treatment adherence suggested maintained functional status in most patients. These outcomes echo findings from Minniti et al. and others, who showed that HFRT can stabilize or improve QoL.

Despite growing evidence, the field still faces limitations: heterogeneity in HFRT regimens, incomplete reporting of key variables (e.g., MGMT status, RT technique), and a lack of consensus on the age threshold defining "elderly." Some define it as ≥60, others ≥70.

Nevertheless, recent analyses suggest that HFRT is suitable even for the "younger elderly" subgroup (65–69 years).

Ongoing trials (e.g., NCT05439278) aim to further clarify the comparative efficacy of standard vs. HFRT regimens. Novel approaches, including temporally modulated pulsed RT, are also being explored to refine treatment strategies.

CONCLUSION:

In this prospective study of elderly GBM patients treated with 40.05 Gy in 15 fractions plus temozolomide, we observed a median OS of 7.99 months and PFS of 5.69 months with acceptable toxicity and preserved neurologic function. These findings, consistent with major trials like Roa et al., support hypofractionated RT as a standard, well-tolerated, and effective option for elderly or frail patients. Future trials should incorporate molecular profiling and QoL assessments to further individualize treatment.

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