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Evaluating the impact of performance status in elderly patients with glioblastoma

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ABSTRACT

Background: Glioblastoma (GBM) is a common brain tumor with a poor prognosis. There is a paucity of knowledge regarding optimal treatment approaches for elderly patients with GBM who have a relatively good Karnofsky (KPS) or Eastern Cooperative Oncology Group (ECOG) performance status. This study compared treatment outcomes in older patients (≥65) with GBM based on their performance status, either high (KPS ≥ 70 and ECOG < 2) or low (KPS < 70 and ECOG ≥ 2), who underwent hypofractionated radiotherapy (HFRT) (40 Gy in 15 fractions) versus conventional fractionation (60 Gy in 30 fractions).

Methods and Materials: Fifty-six patients with newly diagnosed IDH-wildtype GBM were included in this single-institution retrospective analysis. Patient demographics, clinical features, and treatment outcomes were analyzed. Univariable and multivariable Cox regression analyses were used to analyze the association of treatments with overall survival (OS) and progression-free survival (PFS) and the impact of performance status.

Results: Twenty-six patients (46 %) received conventional RT and thirty (54 %) received HFRT. High or low performance status within this patient population did not impact either OS ($p = 0.0532$) or PFS ($p = 0.3054$). For conventionally fractionated RT vs. HFRT, median OS was 13.6 and 6.8 months, respectively, ($p = 0.0034$) and median PFS was 5.98 and 5.55 months respectively, ($p = 0.0488$). Adjuvant temozolomide was significantly associated with improved OS and PFS.

Conclusions: High or low performance status did not affect patient outcomes in this population regardless of RT fractionation. Elderly patients with GBM who received conventionally fractionated RT had superior survival outcomes than those who underwent HFRT and were also more likely to receive concurrent and adjuvant temozolomide. Our findings underscore the impact of systemic therapy in this patient population.

1. Introduction

Glioblastoma (GBM) is the most common brain malignancy in adults and carries a poor prognosis with a median survival of less than 2 years [1,2]. Currently, the standard of care for GBM is maximally safe surgical resection, followed by concurrent chemoradiation and adjuvant chemotherapy with tumor-treating fields [3,4]. The current standard of care for patients < 70 years old with newly diagnosed glioblastoma includes conventionally fractionated radiation therapy to a dose of 60 Gy in 30 fractions over 6 weeks [3,4].

The optimal management of glioblastoma in elderly patients, however, remains controversial. A myriad of factors can complicate an elderly patient's GBM treatment course, precluding them from completing full treatment regimens [5]. Generally, impaired performance status and quality of life, rate of disease progression, and patient choice play a role [5,6]. As a result, many studies in older patients have

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compared short-course radiotherapy (RT) with standard-course RT, showing no difference in survival [5,7–10]. In a prospective randomized clinical trial, Roa et al compared standard RT (60 Gy in 30 fractions over 6 weeks) to short-course RT (40 Gy in 15 fractions over 3 weeks) in patients over 60 years of age with glioblastoma [7]. Patients did not receive chemotherapy unless offered at the time of recurrence. The median survival times of 5.1 months and 5.6 months, respectively, were not significantly different [7]. Similarly, Navarria et al performed a propensity-matched analysis of a control group receiving 60 Gy/30 fractions and a group receiving hypofractionated radiation therapy (HFRT) of 60 Gy/15 fractions [8]. The median OS time of 17.9 months in the control RT group and 16.7 months in the HFRT group were comparable [8]. A multi-institutional cooperative group study randomized patients > 65 year of age (ECOG performance status ≤ 2) with GBM to receive 40 Gy in 15 fractions with vs. without concomitant and adjuvant temozolomide [11]. The addition of temozolomide was associated with longer survival with no detriment in quality of life. Two additional studies corroborate these results using HFRT treatment regimens of 42 Gy/14 fractions and 45 Gy/15 fractions [9,10].

There is currently no standard of care for GBM in patients with poor-performance status. There is not a consensus definition of poor performance for patients with glioblastoma, but many studies define it as Karnofsky Performance Status (KPS) between 50–70 or Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 [5,12–16]. Recent studies have proposed various treatments regiments of RT with or without chemotherapy for glioblastoma in poor performance patients. A 2022 *meta*-analysis evaluated elderly and frail patients with poor performance treated with 52.5 Gy/15 fractions, an HFRT regimen that is calculated to be effective to 60 Gy in 30 fractions [17]. Poor-performing patients, as defined by KPS < 70 in the study, had a median OS of 9.5 months [9]. The median OS of 12.2 months was similarly promising in a retrospective study looking at 56 Gy/20 fractions in poor-performance patients with GBM [15]. A Phase III clinical trial evaluated an even shorter course RT of 25 Gy/5 fractions versus 40 Gy/15 fractions, finding median OS times of 7.9 months and 6.4 months, respectively [18]. Furthermore, HFRT with simultaneous integrated boost (SIB) and temozolomide has been proven effective [13]. A HFRT dose of 40 Gy/15 fractions combined with SIB of 52.5 Gy resulted in a median OS of 13 months [13].

There is a lack of prospective trials comparing conventionally fractionated RT vs. HFRT in elderly patients with GBM and a paucity of literature investigating outcomes of elderly patients with GBM who are optimal performers. Therefore, our study aims to evaluate treatment outcomes of high and low-performance GBM patients who have undergone either HFRT consisting of 40 Gy in 15 fractions or conventionally fractionated RT consisting of 60 Gy in 30 fractions.

2. Methods

A single-institution retrospective analysis was conducted of 56 patients with newly diagnosed GBM who underwent RT from 2020 to 2024 at our institution. Eligible patients were older adults (age ≥ 65 years) with a new diagnosis of IDH-wildtype GBM. Patients were characterized based on their performance status. High-performance status was defined as KPS ≥ 70 and ECOG < 2 and low-performance status as KPS < 70 and ECOG ≥ 2. Overall survival (OS) was defined as the duration from treatment start (surgery) to death from any cause or date of last follow-up. Progression-free survival (PFS) was defined as the duration from treatment to disease progression or death from any cause or date of last follow-up. Univariate Cox regression was used for the univariable analyses of the impact of treatment and demographic/clinical features on OS and PFS. A p-value ≤ 0.05 was considered statistically significant. Variables significant on univariable analyses were included in the multivariable analyses using Cox regression.

For the analysis of overall survival and progression-free survival, patient, tumor, and treatment-related variables were analyzed in a univariate manner. Factors that showed significance in the univariate analyses were then analyzed further using multivariate analysis.

Continuous variables other than performance status were dichotomized into "higher" and "lower" groups based on the median. To address the remaining variables with missing values, a multiple imputation technique was utilized. The results are presented as hazard ratios (HR) with 95 % confidence intervals (CIs). Table 1 demonstrates patient characteristics; the comparison of covariates between conventional fractionation and HFRT arms is included in the survival analysis section. The student *t*-test was conducted for continuous variables, and the Chi-square test was conducted for categorical variables.

Table 1
Patient Population Statistics.

	Conventional Fractionation (N = 26)	Hypo-Fractionation (N = 30)	p-value*
Age			
Mean (SD)	71.7 (5.78)	73.6 (5.91)	0.219
Median [Min, Max]	70.0 [65.0, 89.0]	73.5 [65.0, 87.0]	
KPS Score			
Mean (SD)	73.1 (14.6)	60.7 (12.8)	0.002
Median [Min, Max]	75.0 [40.0, 100]	60.0 [40.0, 80.0]	
ECOG Score			
Mean (SD)	1.08 (0.744)	1.77 (0.679)	<0.001
Median [Min, Max]	1.00 [0, 3.00]	2.00 [1.00, 3.00]	
# of Adjuvant Temozolomide Cycles			
Mean (SD)	4.43 (2.71)	4.64 (3.07)	0.862
Median [Min, Max]	4.00 [1.00, 12.0]	4.00 [1.00, 12.0]	
Missing	12 (46.2 %)	19 (63.3 %)	
Sex			
F	12 (46.2 %)	11 (36.7 %)	0.655
M	14 (53.8 %)	19 (63.3 %)	
Alive as of June 1st, 2024			
N	18 (69.2 %)	25 (83.3 %)	0.353
Y	8 (30.8 %)	5 (16.7 %)	
Extent of Surgery			
Biopsy	3 (11.5 %)	14 (46.7 %)	0.006
GTR	12 (46.2 %)	12 (40.0 %)	
STR	11 (42.3 %)	4 (13.3 %)	
Location of Primary Cancer			
Frontal	5 (19.2 %)	7 (23.3 %)	0.93
other	7 (26.9 %)	9 (30.0 %)	
Parietal	5 (19.2 %)	6 (20.0 %)	
Temporal	9 (34.6 %)	8 (26.7 %)	
MGMT Status			
N	11 (42.3 %)	18 (60.0 %)	0.389
Y	8 (30.8 %)	6 (20.0 %)	
Missing	7 (26.9 %)	6 (20.0 %)	
Received Concurrent Temozolomide			
N	5 (19.2 %)	12 (40.0 %)	0.0946
Y	21 (80.8 %)	15 (50.0 %)	
Missing	0 (0 %)	3 (10.0 %)	
Received Adjuvant Temozolomide			
N	12 (46.2 %)	18 (60.0 %)	0.443
Y	14 (53.8 %)	12 (40.0 %)	
Site of Recurrence			
In Field	14 (53.8 %)	9 (30.0 %)	0.248
L Frontal Parietal	0 (0 %)	1 (3.3 %)	
L Parietal	0 (0 %)	1 (3.3 %)	
R Medial Temporal	0 (0 %)	2 (6.7 %)	
R Parietal and R Temporal	0 (0 %)	1 (3.3 %)	
R Temporal	0 (0 %)	1 (3.3 %)	
L Temporal	1 (3.8 %)	0 (0 %)	
R Corpus Callosum	1 (3.8 %)	0 (0 %)	
Missing	10 (38.5 %)	15 (50.0 %)	

*: p-values are from student *t*-test or Chi-square test.

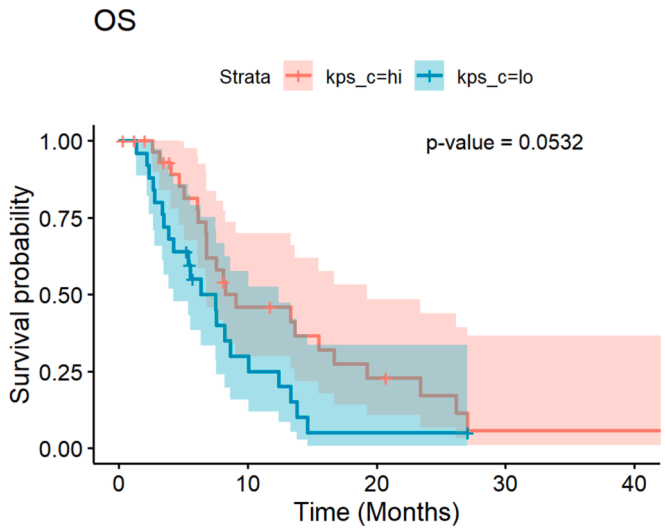

Fig. 1. Impact of Performance Status on Overall Survival.

3. Results

After screening for eligible patients, a total of 56 patients were included in the final analytical population. Patients' demographic and treatment statistics are summarized in Table 1. Median age among the population was 72.0 [65.0, 89.0], over half of whom were male 33 (58.9 %). Twenty-six patients (46 %) received conventional RT over 6 weeks (60 Gy/30 fractions) and thirty (54 %) received HFRT over 3 weeks (40 Gy/15 fractions). Patients who had HFRT tended to be older with an average age of 73.6 (SD 5.91) compared to those who had conventionally fractionated RT with an average age of 71.7 (SD 5.78). HFRT patients had a lower reported median KPS score of 60 [40,80] and higher median ECOG score of 2 [1,3] compared to conventionally fractionated RT patients (75 [40,100] and 1 [0,3], respectively). HFRT patients were also less likely to receive concurrent TMZ (HFRT: 50.0 % vs CF RT: 80.8 %) and adjuvant TMZ (HFRT: 40.0 % vs CF RT: 53.8 %). MGMT methylation status, reason for stopping TMZ, tumor location, and site of recurrence were all not significantly different between the groups. Extent of surgery prior to radiation was significantly different between the groups ($p = 0.006$).

The patient population was stratified into high performance status group (KPS score ≥ 70) and low performance status group (KPS < 70). The median OS of the patients with high performance status was 8.67 months (95 % CI: [6.80, 19.3]), versus 7.49 months (95 % CI: [4.24, 12.4]) for the low performance status cohort, shown in Fig. 1 (p-value of log-rank test is $= 0.0532$). The shading area in Fig. 1–4 represents the 95 % confidence interval for the survival time. The median progression-free survival for the high and low performance cohorts were 6.11 (95 % CI: [4.63, 7.66]) and 4.63 (95 % CI: [2.66, 7.56]), respectively (p-value of log-rank test is $= 0.3054$), shown in Fig. 2.

The median OS for patients treated with conventional fractionation vs. HFRT was 13.6 months (95 % CI: [6.80, 23.39]) and 6.8 months (95 % CI: [5.55, 8.61]), respectively, (p-value of log-rank test is 0.0034) (Fig. 3). The median PFS for patients treated with conventional fractionation vs. HFRT was 5.98 months (95 % CI: [4.63, 11.20]) and 5.55 months (95 % CI: 2.66, 6.83]), respectively, (p-value of log-rank test is 0.0488) (Fig. 4).

Univariate analysis demonstrated HFRT was significantly associated with worse OS ($p = 0.0044$) (Table 2). Multivariate analysis confirmed HFRT was significantly associated with worse OS ($p = 0.0018$) and adjuvant temozolomide also significantly impacted OS ($p = 0.004$) (Table 3**)**. Univariable analysis demonstrated that low performance status was not associated with worse OS ($p = 0.0572$). HFRT ($p = 0.0203$) and adjuvant temozolomide ($p = 0.0060$) were significantly associated with PFS in multivariate analysis (Tables 4 and 5). Performance status does not significantly impact overall survival or progression-free survival across the two fractionation groups (Tables 6 and 7). Within each treatment arm, high and low performance statuses were shown to have no effect on OS ($p_{conventional} = 0.667$ and $p_{hypo} = 0.810$) or PFS ($p_{conventional} = 0.943$ and $p_{hypo} = 0.676$), illustrated in **Supplementary Table S1**. Conversely, within high or low performance status groups, treatment (conventional/hypo Fx) was found to have no

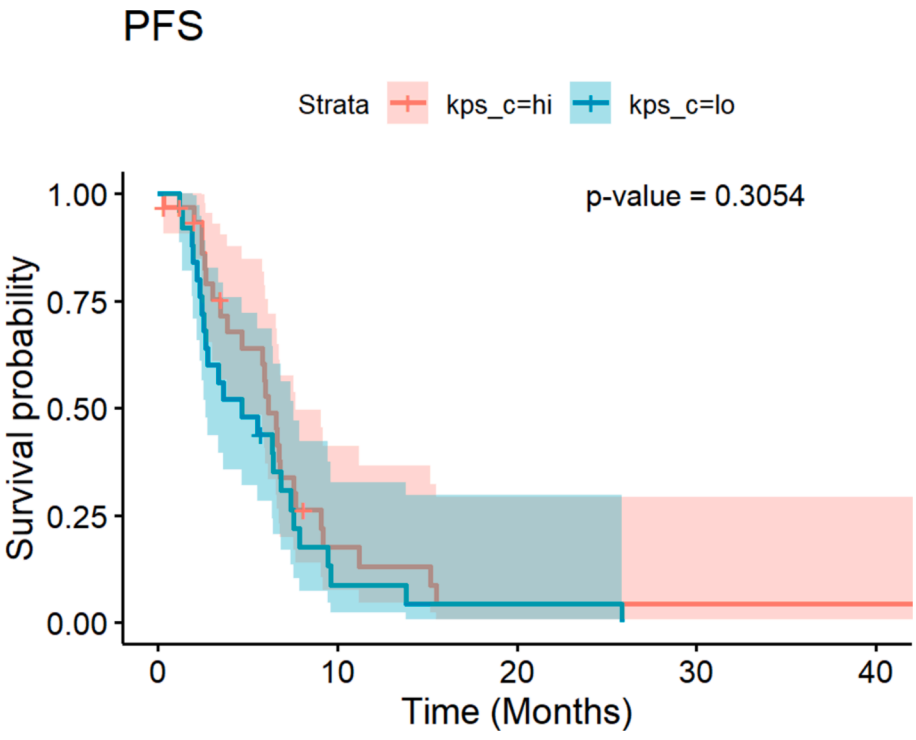

Fig. 2. Impact of Performance Status on Progression-Free Survival.

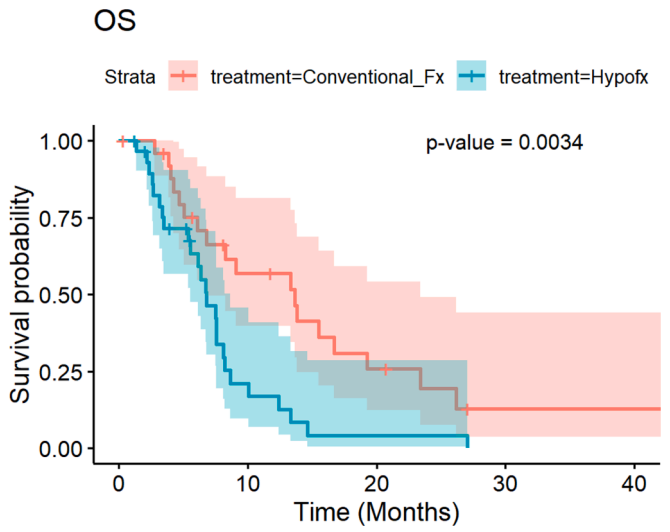

Fig. 3. Comparison of Overall Survival Between Conventional Fractionation (CF) vs Hypofractionated Radiation Therapy (HFRT).

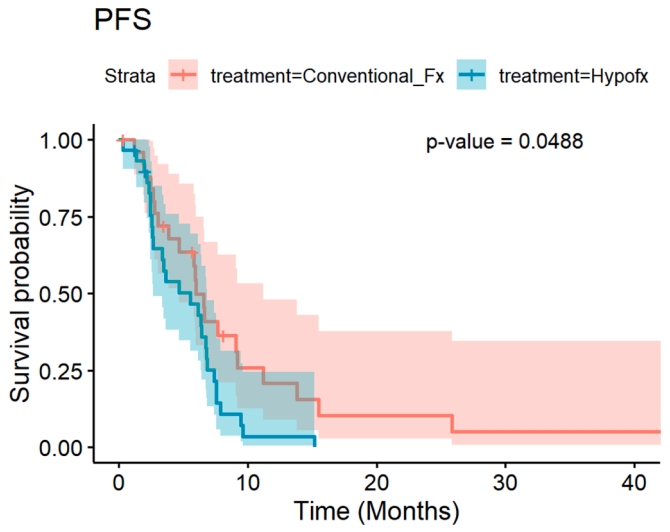

Fig. 4. Comparison of Progression-Free Survival Between Conventional Fractionation (CF) vs. Hypofractionated Radiation Therapy (HFRT).

significant effect on OS ($p_{highKPS} = 0.017$ and $p_{lowKPS} = 0.2628$) or PFS ($p_{highKPS} = 0.335$ and $p_{lowKPS} = 0.159$) (**Supplementary Table S2**).

4. Discussion

This retrospective study analyzed the outcomes of elderly patients with high and low performance status treated with radiotherapy for GBM with conventional fractionation or HFRT at 40 Gy/15 fractions. Patients in our population treated with HFRT had significantly worse OS (6.8 months) compared to patients who underwent conventional RT (13.3 months). Previous literature evaluating outcomes in all age groups with newly diagnosed GBM demonstrated no significant difference in OS for patients receiving HFRT compared to conventional RT, underscoring the impact of patient age and the complex challenge of elderly patients with GBM [8–10]. Our HFRT overall survival results are concordant with previous literature that specifically investigated outcomes in elderly patients with GBM; Roa et al reported an OS of 5.6 months after HFRT and Perlow et. al found an OS of 10.3 months after HFRT [7,10]. The HFRT regimen was 40 Gy/15 fractions in both our study and Roa et. al, while Perlow et. al evaluated HFRT at 52.5 Gy/15 fractions, which

Table 2
Univariate Analysis of Treatment Variables with Overall Survival.

Variable	Value	Hazard Ratio (95 % CI)	p-value
Treatment Type	Conventional Fractionation	–	
	Hypo-Fractionation	2.51 (1.33, 4.73)	0.004
Age	>= 70	–	
	< 70	0.57 (0.31, 1.06)	0.078
KPS Score	>= 70	–	
	< 70	1.81 (0.98, 3.34)	0.057
ECOG Score	>= 2	–	
	< 2	0.55 (0.3, 1.02)	0.057
# of Adjuvant Temozolomide Cycles	>= 4	–	
	< 4	1.52 (0.61, 3.77)	0.372
sex	Female	–	
	Male	0.82 (0.45, 1.52)	0.534
Extent of Surgery	Biopsy	–	
	GTR	0.76 (0.37, 1.57)	0.463
	STR	0.54 (0.24, 1.22)	0.139
Location of Primary Cancer	Frontal	–	
	other	1.73 (0.69, 4.32)	0.242
	Parietal	0.92 (0.32, 2.65)	0.873
	Temporal	1.52 (0.62, 3.74)	0.359
Received Concurrent Temozolomide	N	–	
	Y	0.33 (0.17, 0.65)	0.001
MGMT Status	N	–	
	Y	0.84 (0.37, 1.87)	0.663
Received Adjuvant Temozolomide	N	–	
	Y	0.26 (0.13, 0.52)	< 0.001

Table 3
Multivariate Analysis of Treatment Variables with Overall Survival.

Variable	Estimate	p-value	HR (95 % CI)
Hypo-Fractionated Treatment	1.168	0.002	3.21 (1.63, 6.34)
Received Concurrent Temozolomide (Y)	−0.184	0.684	0.832 (0.347, 1.999)
Received Adjuvant Temozolomide (Y)	−1.461	0.004	0.232 (0.091, 0.590)

could account for the slight difference in reported OS. Our study also shows that PFS is worse in patients treated with HFRT (5.55 months) than conventional RT (5.98 months) [17]. Rayan et. al reported similar findings in their prospective study comparing HFRT and standard RT with concurrent temozolomide, with PFS of 7.3 months and 9.9 months, respectively [10]. However, the difference reported was not statistically significant [10].

We report for the first time, to the best of our knowledge, no change in overall survival outcomes associated with high-performance status in elderly patients with GBM. Slotman et al. reported the favorable prognostic factors for GBM patients as age < 50, KPS 80–100, and ≥ 75 % tumor removal and poor prognostic factors as age ≥ 50, KPS ≤ 70, and < 75 % tumor removal [9]. Patients with all 3 favorable prognostic factors had a median survival of 50 weeks, while those with 1 or 2 favorable prognostic factors had a median survival or 38 weeks [9]. Our study reported median OS in high and low performing patients as 8.67 months (38 weeks) and 7.49 months (33 weeks), respectively, underscoring the impact of the advanced age in our elderly patient population and the crucial role of systemic therapy in the treatment management of these patients.

Prior studies have shown that concurrent or adjuvant chemotherapy improves survival outcomes for GBM patients. Perlow et. al reports concurrent temozolomide as an independent prognostic factor for improved OS and progression-free survival (PFS) in GBM patients

Table 4
Univariate Association of Treatment Variables with PFS.

Variable	Value	Hazard Ratio (95 % CI)	p-value
Treatment Type	Conventional Fractionation	–	
	Hypo-Fractionation	1.8 (1, 3.27)	0.052
Age	High	–	
	Low	0.68 (0.38, 1.22)	0.193
KPS Score	High	–	
	Low	1.34 (0.76, 2.35)	0.307
ECOG Score	High	–	
	Low	0.75 (0.43, 1.31)	0.307
# of Adjuvant Temozolomide Cycles	High	–	
	Low	1.83 (0.78, 4.28)	0.166
sex	Female	–	
	Male	1.16 (0.64, 2.11)	0.615
Extent of Surgery	Biopsy	–	
	GTR	0.94 (0.47, 1.88)	0.868
	STR	1.02 (0.49, 2.11)	0.965
Location of Primary Cancer	Frontal	–	
	other	1.5 (0.65, 3.48)	0.346
	Parietal	1.26 (0.5, 3.19)	0.625
	Temporal	1.18 (0.51, 2.74)	0.692
Received Concurrent Temozolomide	N	–	
	Y	0.64 (0.35, 1.18)	0.152
MGMT Status	N	–	
	Y	0.71 (0.33, 1.51)	0.375
Received Adjuvant Temozolomide	N	–	
	Y	0.48 (0.27, 0.86)	0.013

Table 5
Multivariable Association of Treatment Variables With PFS.

Variable	Estimate	p-value	HR (95 % CI)
Hypo-Fractionated Treatment	0.771	0.020	2.16 (1.153, 4.050)
Received Adjuvant Temozolomide (Y)	−0.887	0.006	0.412 (0.225, 0.754)

Table 6
Analysis of Impact of Performance Status on OS.

	Estimate	HR (95 % CI)	p-value
KPS Score (Low)	0.228	1.256 (0.409, 3.858)	0.690
Hypo-Fractionated Treatment	0.792	2.208 (0.908, 5.369)	0.081
KPS Score (Low): Hypo-Fractionated Treatment	0.057	1.058 (0.251, 4.465)	0.939

Table 7
Analysis of Impact of Performance Status on PFS.

	Estimate	HR (95 % CI)	p-value
KPS Score (Low)	−0.093	0.911 (0.327, 2.538)	0.859
Hypo-Fractionated Treatment	0.448	1.566 (0.684, 3.586)	0.289
KPS Score (Low): Hypo-Fractionated Treatment	0.283	1.327 (0.357, 4.935)	0.672

treated with HFRT of 52.5 Gy/15 fractions [17]. Beckham et. al demonstrated a significantly improved PFS and OS in GBM patients receiving HFRT and adjuvant temozolomide compared to patients treated with only HFRT [19]. We reported a significant association between adjuvant temozolomide and both overall survival and progression-free survival.

This current study has several limitations. As a retrospective, single-center study, there may be unrecognized biases that were unable to be addressed by the analysis. Future prospective trials are necessary in order to investigate outcomes of elderly patients with GBM who are optimal performers. Further studies are necessary in order to provide more definitive data on management of elderly patients with GBM, particularly for those who are high performers and may benefit from an aggressive treatment regimen.

CRediT authorship contribution statement

Neil D. Almeida: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Julia Rupp:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Babar Gulzar:** Writing – review & editing, Validation, Project administration, Methodology, Investigation, Formal analysis. **Tyler V. Schrand:** Writing – original draft, Visualization, Validation, Software, Investigation, Data curation. **Venkatesh Madhugiri:** Writing – review & editing, Validation, Investigation, Formal analysis. **Mengyu Fang:** Writing – review & editing, Validation, Supervision, Investigation, Formal analysis, Data curation. **Rohil Shekher:** Writing – review & editing, Visualization, Validation, Methodology, Investigation, Conceptualization. **Victor Goulenko:** Writing – review & editing, Validation, Investigation, Data curation. **Divya Goyal:** Writing – original draft, Validation, Data curation, Conceptualization. **Shefalika Prasad:** Validation, Software, Methodology, Data curation, Conceptualization. **Michael T. Milano:** Writing – review & editing, Validation, Supervision, Conceptualization. **Dheerendra Prasad:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2024.111028.

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