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Early Initiation of Radiation Therapy Improves Survival in Elderly Patients With Glioblastoma

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BACKGROUND AND OBJECTIVES: To study the impact of early initiation of radiation therapy (RT) in elderly patients with newly diagnosed glioblastoma.

METHODS: A total of 56 elderly patients (aged 65 and older) diagnosed with isocitrate dehydrogenase (IDH)-wildtype glioblastoma were analyzed from a prospective registry from 2020 to 2024. Survival analysis was conducted to evaluate the impact of timing of RT initiation after surgical resection on survival outcomes. A specific cutoff point for RT initiation was evaluated using the log-rank test, with *P*-values adjustment for multiple comparisons using the false discovery rate approach. Kaplan-Meier curves were used to illustrate survival distributions. Associations of various risk factors with survival were initially examined through univariate Cox regression models, followed by multivariate analysis to assess the combined effects of these factors. The results were reported as hazard ratios with 95% CIs.

RESULTS: Elderly patients with glioblastoma who underwent initiation of RT < 20 days from date of surgery demonstrated improved overall survival (OS) (*P* = .0460) and progression-free survival (PFS) (*P* = .0075) in our cohort. Multivariate analysis demonstrated that adjuvant temozolomide significantly affected both OS (*P* = .0038) and PFS (*P* = .0133). Conventionally fractionated RT consisting of 60 Gy in 30 fractions demonstrated significantly improved PFS (*P* = .0164) in patients who underwent early initiation of RT (<20 days). By contrast, hypofractionated RT delivering 40 Gy in 15 fractions did not show significantly improved PFS (*P* = .0509) in patients who underwent early initiation of RT (<20 days).

CONCLUSION: Early initiation of RT in elderly patients with newly diagnosed glioblastoma improves both OS and progression-free survival. Timing of RT is particularly of significance in this patient population who may not be optimal candidates for systemic chemotherapy.

KEY WORDS: Elderly, Glioblastoma multiforme, Chemoradiation

Glioblastoma is the most common fatal primary brain tumor in adults, and despite standard of care, median overall survival (OS) remains approximately 15 months.^{1,2} Glioblastoma management is based on maximal safe surgical

resection followed by concurrent radiotherapy and chemotherapy with temozolomide (TMZ) with adjuvant daily TMZ and tumor treating fields (TTFields) after radiation.³ Elderly patients with glioblastoma are a unique patient cohort who are significantly

ABBREVIATIONS: HR, hazard ratio; KPS, Karnofsky Performance Status; OS, overall survival; RT, radiation therapy; TMZ, temozolomide.

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TABLE 1. Patients Characteristics

	RT < 20 d (n = 38)	RT ≥ 20 d (n = 18)	P-value ^a
Age			
Mean (SD)	72.3 (5.89)	73.5 (5.95)	.49
Median (Min, Max)	72.0 (65.0, 89.0)	72.0 (65.0, 87.0)	
KPS score			
Mean (SD)	70.8 (11.7)	57.2 (17.1)	.0054
Median (Min, Max)	70.0 (50.0, 90.0)	50.0 (40.0, 100)	
ECOG score			
Mean (SD)	1.21 (0.622)	1.94 (0.873)	.0036
Median (Min, Max)	1.00 (0, 2.00)	2.00 (0, 3.00)	
No. of adjuvant temozolomide cycles			
Mean (SD)	4.73 (2.83)	3.00 (2.65)	.379
Median (Min, Max)	4.00 (1.00, 12.0)	2.00 (1.00, 6.00)	
Missing	16 (42.1%)	15 (83.3%)	
Sex			
Female	15 (39.5%)	8 (44.4%)	.95
Male	23 (60.5%)	10 (55.6%)	
Alive as of June 1, 2024			
No	28 (73.7%)	15 (83.3%)	.646
Yes	10 (26.3%)	3 (16.7%)	
Surgery received			
Biopsy	14 (36.8%)	3 (16.7%)	.266
GTR	14 (36.8%)	10 (55.6%)	
STR	10 (26.3%)	5 (27.8%)	
Location of primary cancer			
Frontal	8 (21.1%)	4 (22.2%)	.941
Other	10 (26.3%)	6 (33.3%)	
Parietal	8 (21.1%)	3 (16.7%)	
Temporal	12 (31.6%)	5 (27.8%)	
MGMT status			
No	21 (55.3%)	8 (44.4%)	1
Yes	10 (26.3%)	4 (22.2%)	
Missing	7 (18.4%)	6 (33.3%)	
Received concurrent temozolomide			
No	8 (21.1%)	9 (50.0%)	.0547
Yes	28 (73.7%)	8 (44.4%)	
Missing	2 (5.3%)	1 (5.6%)	

TABLE 1. Continued.

	RT < 20 d (n = 38)	RT ≥ 20 d (n = 18)	P-value ^a
Received adjuvant temozolomide			
No	16 (42.1%)	14 (77.8%)	.0269
Yes	22 (57.9%)	4 (22.2%)	
Site of recurrence			
In field	16 (42.1%)	7 (38.9%)	.491
L frontal parietal	0 (0%)	1 (5.6%)	
L parietal	1 (2.6%)	0 (0%)	
R medial temporal	1 (2.6%)	1 (5.6%)	
R parietal and R temporal	1 (2.6%)	0 (0%)	
R temporal	1 (2.6%)	0 (0%)	
L temporal	1 (2.6%)	0 (0%)	
R corpus callosum	0 (0%)	1 (5.6%)	
Missing	17 (44.7%)	8 (44.4%)	
Pre-operative tumor volume (cm³)			
Mean (SD)	33.8 (27.7)	36.8 (29.5)	.717
Median (Min, Max)	26.0 (0.310, 110)	33.5 (8.46, 131)	
Brainstem/basal ganglia involvement			
No	28 (73.7%)	14 (77.8%)	1
Yes	10 (26.3%)	4 (22.2%)	
pre_op_midline_shift			
Mean (SD)	2.12 (3.45)	2.28 (2.72)	.852
Median (Min, Max)	0 (0, 13.0)	0.600 (0, 7.10)	
Missing	0 (0%)	2 (11.1%)	
post_op_midline_shift			
Mean (SD)	1.32 (2.59)	1.74 (2.34)	.545
Median (Min, Max)	0 (0, 10.0)	0 (0, 6.40)	
Missing	2 (5.3%)	0 (0%)	
pre_op_edema			
Mean (SD)	85.2 (63.6)	84.5 (54.1)	.967
Median (Min, Max)	80.8 (6.76, 222)	83.9 (4.38, 204)	
Missing	1 (2.6%)	2 (11.1%)	
post_op_edema			
Mean (SD)	69.9 (50.6)	68.2 (31.1)	.88
Median (Min, Max)	71.4 (7.83, 196)	69.2 (18.2, 119)	
Missing	1 (2.6%)	0 (0%)	

TABLE 1. Continued.

	RT < 20 d (n = 38)	RT ≥ 20 d (n = 18)	P-value ^a
Bilateral involvement			
Yes	9 (23.7%)	3 (16.7%)	.803
No	29 (76.3%)	15 (83.3%)	
Median (Min, Max)	71.4 (7.83, 196)	69.2 (18.2, 119)	
Missing	1 (2.6%)	0 (0%)	

ECOG, Eastern Cooperative Oncology Group; GTR, gross total resection; KPS, Karnofsky Performance Status; MGMT, 06-methylguanine-DNA methyltransferase; RT, radiation therapy; STR, subtotal resection.

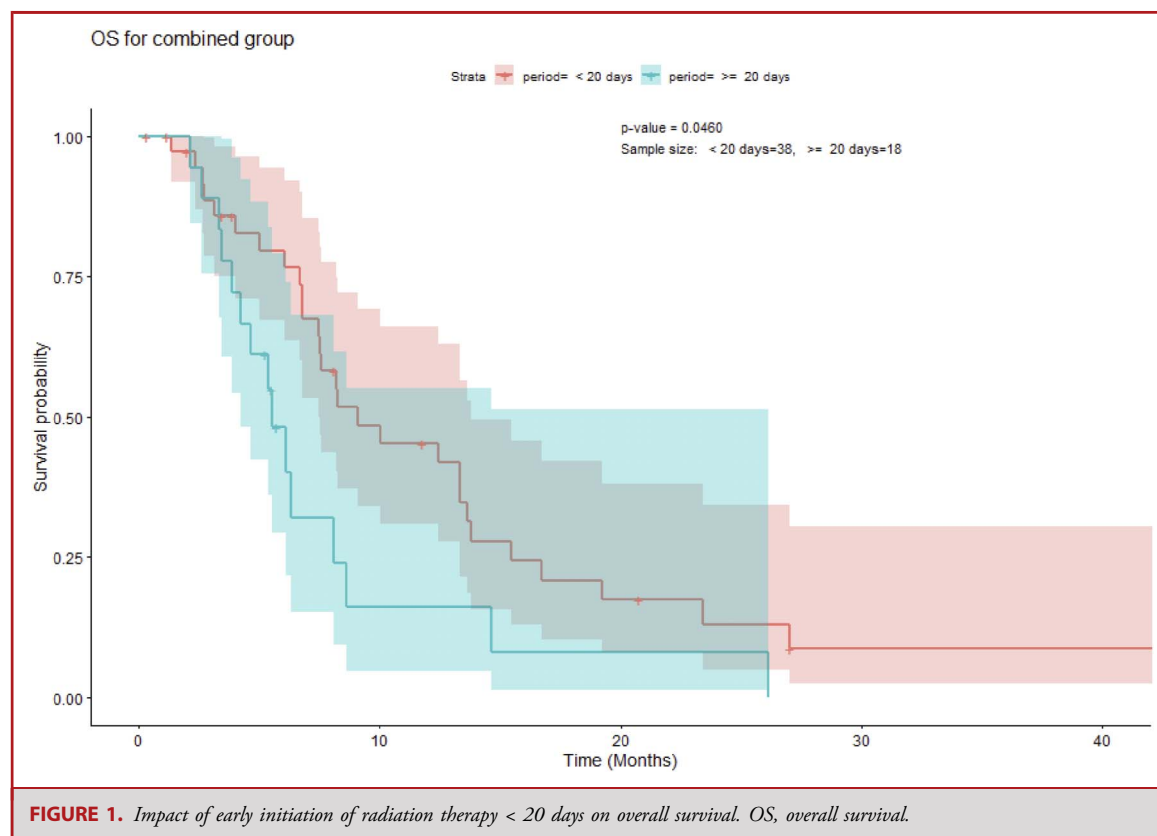
^aP-values are from Student *t*-test or χ^2 test.

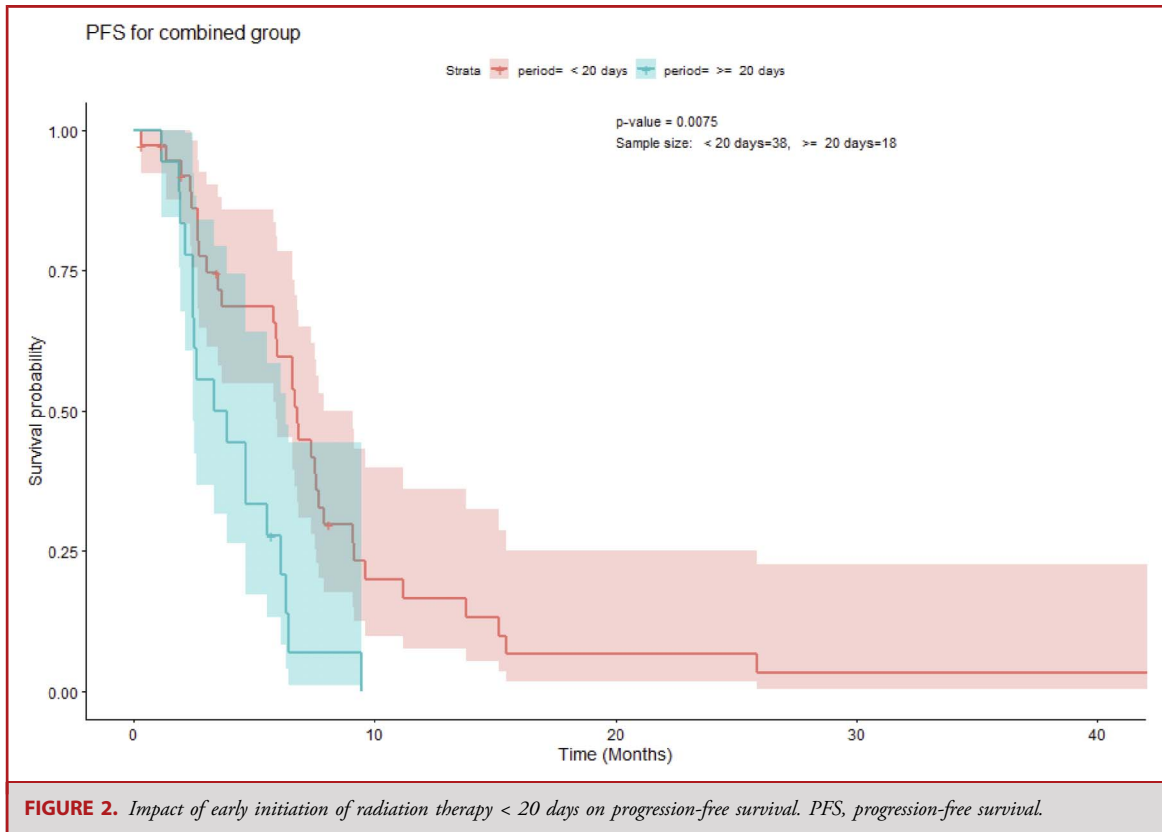
affected by the progressive neurological deficits and loss of cognitive function due to the tumor burden.^{4,5}

A critical management goal of aggressive gliomas is minimizing the delay to initiation of radiation therapy (RT) from surgical intervention.⁶ Previous authors have demonstrated that delays in radiotherapy result in a clinically significant reduction in survival in patients with high-grade glioma, with risk of death increased by 1.2% for each day of waiting from surgery to RT.⁷

Authors have reported that delay in initiation of postoperative chemoradiotherapy beyond 6 weeks is associated with worsened survival in patients with glioblastoma.⁸ The optimal time point of initiation of RT before this 6-week cutoff point is currently a matter of debate and has not been investigated to date in elderly patients with newly diagnosed glioblastoma.

Prior authors have postulated that concurrent TMZ has an additive or synergistic/radiosensitizing mechanism, which allows





for the timing of RT to be less significant.⁹ We speculate that even without the synergy of TMZ in elderly patients who may not be a candidate for systemic therapy, the timing of initiating (chemo) radiation is paramount and underscores the impact of early RT.

Here, we highlight our institution's experience regarding the significance of timing of RT after surgical intervention in elderly patients with newly diagnosed glioblastoma.

METHODS

This retrospective cohort study was conducted using data extracted from a prospective patient registry. The study population consisted of 56 elderly patients, defined as those aged 65 years and older, with a new diagnosis of isocitrate dehydrogenase (IDH)-wildtype glioblastoma who underwent surgical resection followed by RT. Treatment modalities for these patients were categorized into 2 primary RT fractionation schemes: hypofractionated RT, 40 Gy in 15 fractions, or conventionally fractionated RT, 60 Gy in 30 fractions. The distribution of treatment types among the elderly patients revealed that 26 received conventionally fractionated RT, while 30 were treated with hypofractionated RT.

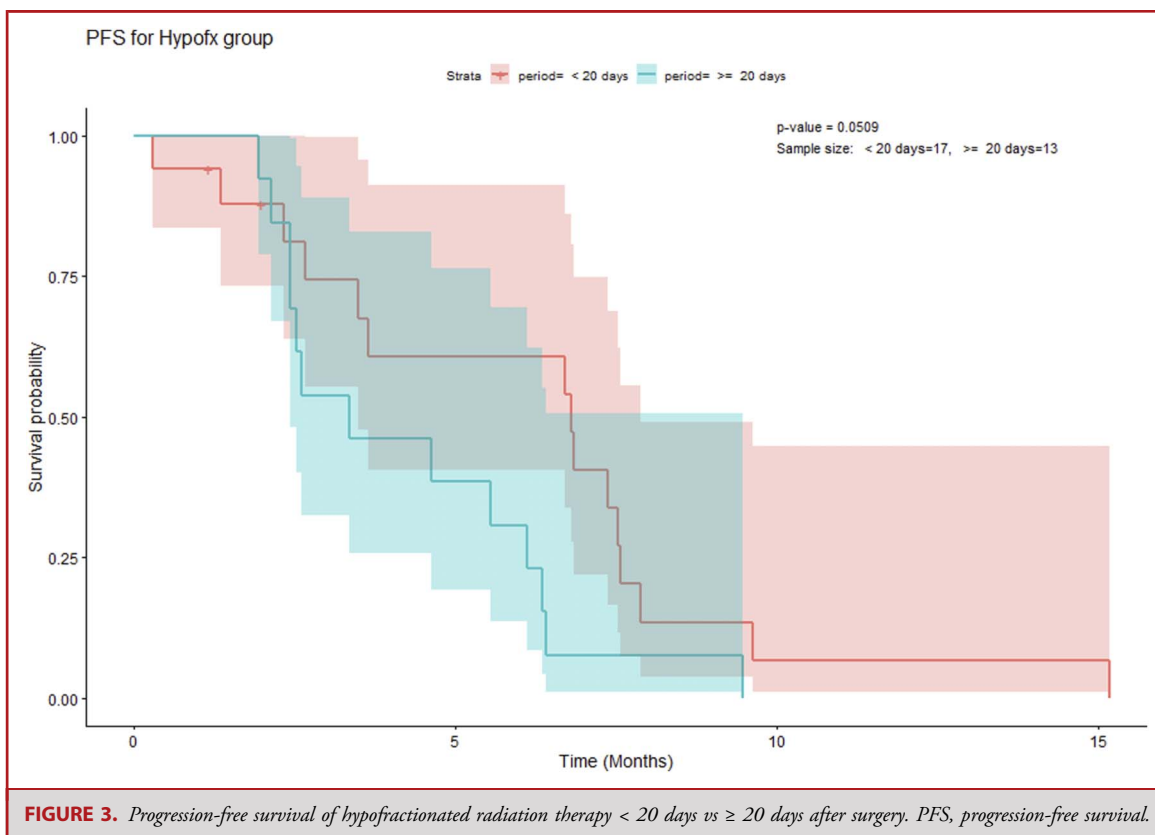
Patient demographics, clinical characteristics, surgical details, RT initiation dates, and follow-up outcomes were obtained from the registry. The primary end points of the study were OS and progression-free survival (PFS). OS was defined as the time from surgery to death from any cause, and PFS was defined as the time from surgery to disease progression or death, whichever occurred first.

Statistical Analysis

Survival analysis was performed to assess the impact of the timing of RT initiation on OS and PFS. Patients were categorized based on the number of days from surgery to the start of RT, with specific cutoff points evaluated to determine their impact on survival outcomes. Cutoff points for RT initiation were investigated and Kaplan-Meier survival curves generated to illustrate survival distributions. The log-rank test, adjusted for multiple comparisons using the Benjamini-Hochberg False Discovery Rate method, assessed significance in survival differences between groups, with a *P*-value threshold of less than 0.05. The relationship between overall survival and the timing of RT initiation, alongside other clinical variables, was assessed using univariate Cox regression analyses. The clinical variables considered included the extent of surgical resection, concurrent temozolomide, 06-methylguanine-DNA methyltransferase promoter methylation status, and adjuvant temozolomide, which were confirmed at baseline. Subsequently, a multivariate Cox regression analysis was conducted to evaluate the combined impact of these variables on survival outcomes. To assess the effect of several prognostic variables, including performance status, adjuvant temozolomide, preoperative tumor volume, and brainstem/basal ganglia involvement, on overall survival within early and late RT groups, a Cox regression analysis incorporating an interaction term was performed. The results are reported as hazard ratios (HRs) with accompanying 95% confidence intervals (CIs).

Institutional Review Board Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work have



been appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) as well as the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. The study was approved by the institutional review board (EDR-103707). The IRB has agreed that individual consent is not needed.

RESULTS

Patient demographics are presented in Table 1. Patients who initiated RT < 20 days after surgery demonstrated significantly higher OS than patients who received RT ≥ 20 days ($P = .0460$). In addition, patients who initiated RT < 20 days after surgery had significantly improved progression-free survival than patients who underwent RT ≥ 20 days postoperatively ($P = .0075$). These results are illustrated in Figures 1 and 2, respectively. There was no observed disease progression in our study before the initiation of radiotherapy in the cohort of patients treated beyond 20 days from surgery. The impact of fractionation of RT (hypofractionation vs conventional fractionation) on PFS among patients who underwent early initiation of RT (<20 days) is shown in Figure 3 ($P = .0509$) and Figure 4 ($P = .0164$), respectively.

In the univariate Cox regression analysis, delayed initiation of RT was significantly associated with worse overall survival (HR =

2.04, 95% CI: 1.07-3.9, $P = .0312$) from Figure 5 and worse progression-free survival (HR = 2.83, 95% CI: 1.48-5.41, $P = .0017$) from Figure 6. However, in the multivariate model adjusting for other variables including performance status (Karnofsky Performance Status [KPS] score), adjuvant temozolomide, the association between RT timing and overall survival or progression-free survival was no longer statistically significant ($P = .2962$ and $P = .0670$, respectively, Tables 2 and 3).

We further included an interaction term between RT timing and performance status in the Cox regression model to evaluate potential effect modification. However, the interaction term was not statistically significant ($P = .927$, **Supplemental Digital Content 1** [<http://links.lww.com/NEU/F46>]) nor were the main effects of RT timing or performance status. These results suggest that the association between RT initiation and overall survival does not differ significantly by performance status.

In addition, univariate analysis demonstrated that both concurrent temozolomide and adjuvant temozolomide were significantly associated with improved overall survival ($P = .0012$ and $P = .0001$, Figure 5). Multivariate analysis confirmed that adjuvant temozolomide significantly affected overall survival ($P = .0127$, Table 2). Similarly, in both the univariate analysis and multivariate analysis for PFS, the adjuvant temozolomide was significantly associated with the PFS ($P = .0127$ and $P = .0133$, respectively, Figure 6 and Table 3).

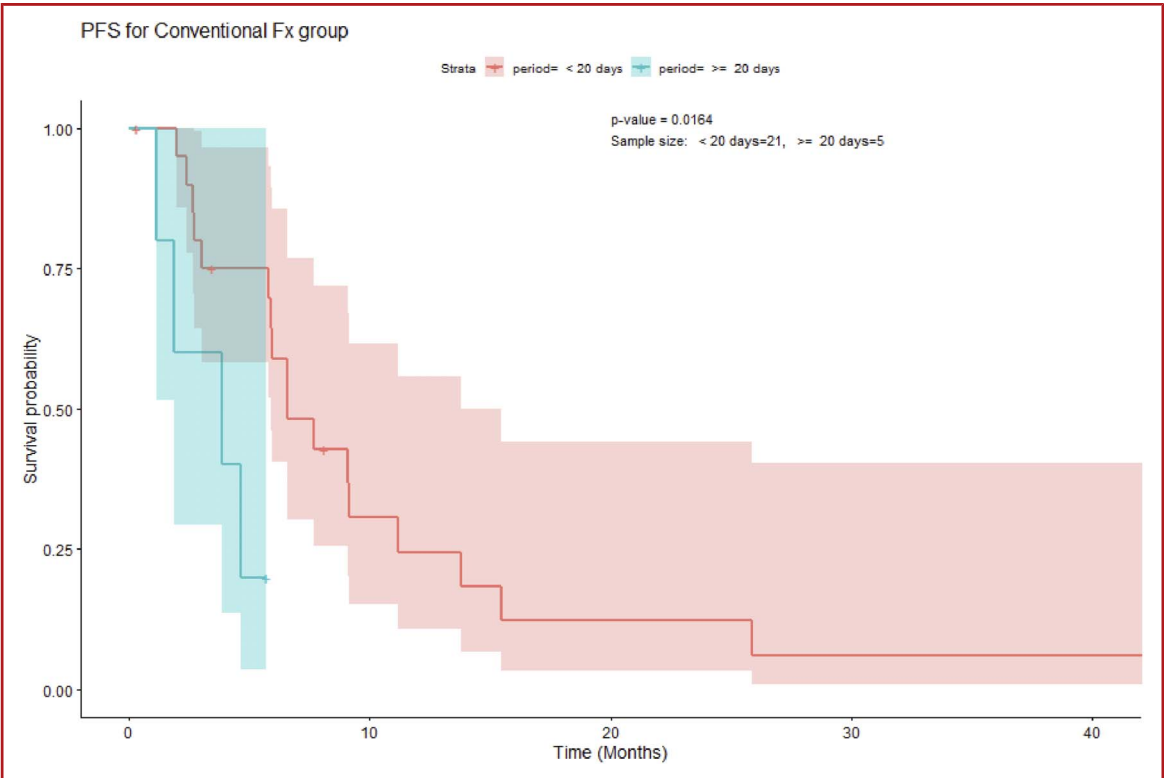


FIGURE 4. Progression-free survival of conventionally fractionated radiation therapy < 20 days vs ≥ 20 days after surgery. PFS, progression-free survival.

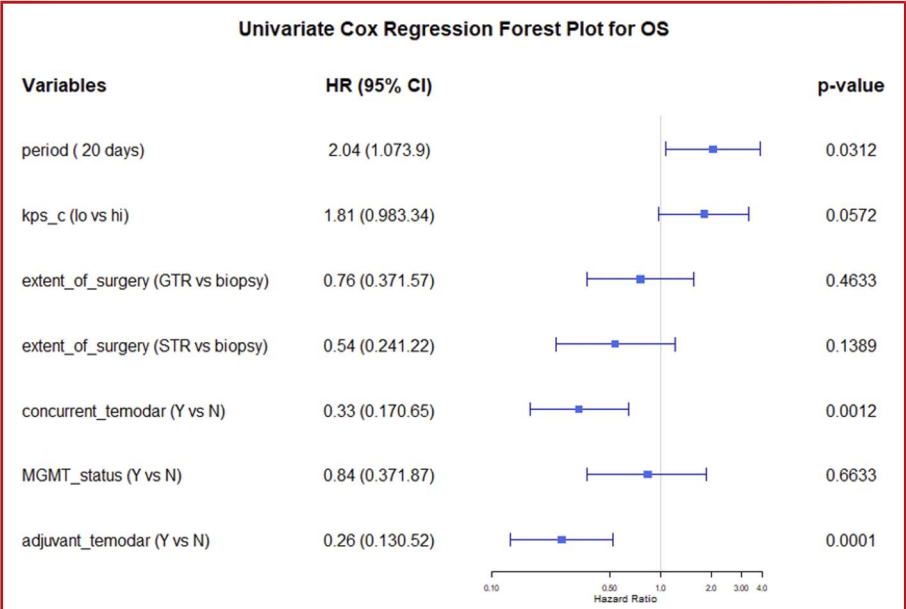
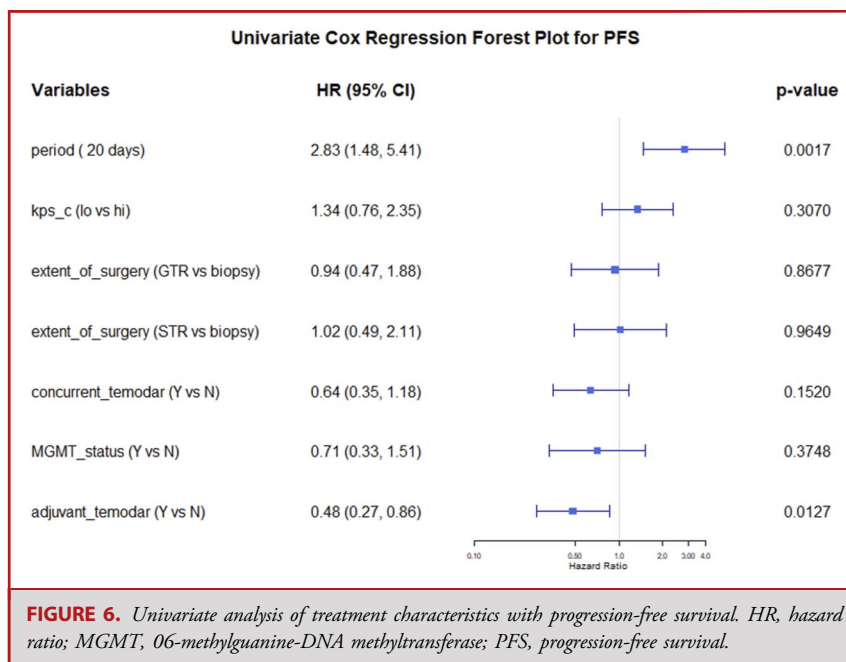


FIGURE 5. Univariate analysis of treatment characteristics with overall survival. HR, hazard ratio; MGMT, 06-methylguanine-DNA methyltransferase; OS, overall survival.



The results of Cox regression model indicated that the adjuvant temozolomide, preoperative tumor volume, and brainstem or basal ganglia involvement did not significantly affect overall survival across the early or late RT groups ($P = .1533$, $P = .4368$, and $P = .9163$, respectively, **Supplemental Digital Content 2** [http://links.lww.com/NEU/F47], **Supplemental Digital Content 3** [http://links.lww.com/NEU/F48], and **Supplemental Digital Content 4** [http://links.lww.com/NEU/F49]).

A subgroup analysis has been performed to check the effect of timing of RT in different groups. It showed that there are significant differences of overall survival between the early and late

RT group in the high preoperative midline shift, high postoperative midline shift, low preoperative edema, bilateral involvement (no) groups, and tumor volume (**Supplemental Digital Content 5** [http://links.lww.com/NEU/F50], **Supplemental Digital Content 6** [http://links.lww.com/NEU/F51], **Supplemental Digital Content 7** [http://links.lww.com/NEU/F52], **Supplemental Digital Content 8** [http://links.lww.com/NEU/F53], **Supplemental Digital Content 9** [http://links.lww.com/NEU/F54], **Supplemental Digital Content 10** [http://links.lww.com/NEU/F55], and **Supplemental Digital Content 11** [http://links.lww.com/NEU/F56]).

TABLE 2. Multivariate Analysis of Treatment Characteristics With Overall Survival

Variable	Estimate	HR (95% CI)	P-value
Timing of RT (≥20 d)	0.5411	1.72 (0.62, 4.74)	.2962
KPS score (Low)	0.7400	2.10 (0.82, 5.33)	.1201
Extent of surgery (GTR)	−1.0162	0.36 (0.11, 1.20)	.0968
Extent of surgery (STR)	−1.0126	0.36 (0.12, 1.13)	.0793
Concurrent temozolomide (Y)	−0.2293	0.80 (0.23, 2.70)	.7133
MGMT status (Y)	−0.3783	0.69 (0.29, 1.62)	.3906
Adjuvant temozolomide (Y)	−1.8153	0.16 (0.05, 0.55)	.0038

GTR, gross total resection; HR, hazard ratio; KPS, Karnofsky Performance Status; MGMT, 06-methylguanine-DNA methyltransferase; RT, radiation therapy; STR, subtotal resection.

TABLE 3. Multivariate Analysis of Treatment Characteristics With Progression-Free Survival

Variable	Estimate	HR (95% CI)	P-value
Timing of RT (≥20 days)	0.8918	2.44 (0.94, 6.33)	.0670
KPS score (Low)	0.4330	1.54 (0.65, 3.67)	.3276
Extent of Surgery (GTR)	−0.5639	0.57 (0.20, 1.63)	.2934
Extent of Surgery (STR)	−0.3232	0.72 (0.27, 1.94)	.5202
Concurrent Temozolomide (Y)	0.3435	1.41 (0.47, 4.26)	.5425
MGMT status (Y)	−0.4263	0.65 (0.30, 1.42)	.2820
Adjuvant Temozolomide (Y)	−1.3122	0.27 (0.10, 0.76)	.0133

GTR, gross total resection; HR, hazard ratio; KPS, Karnofsky Performance Status; MGMT, 06-methylguanine-DNA methyltransferase; RT, radiation therapy; STR, subtotal resection.

DISCUSSION

Elderly patients with newly diagnosed glioblastoma present a unique challenge for management due to their functional deficits, multiple medical comorbidities, and vulnerability to treatment-related toxicity.¹⁰ Optimizing treatment outcomes in this patient population entails maximizing the therapeutic benefit of RT. There is a paucity of data regarding outcomes of elderly patients with newly diagnosed glioblastoma and the impact of timing to RT from surgery.

The impact of RT timing on glioblastoma outcomes has demonstrated varying results in the literature.^{11,12} The bulk of the current data demonstrates a survival detriment with delaying RT postsurgery.^{7,13-16} These findings have molded the current National Comprehensive Cancer Network¹⁷ recommendation that an RT initiation within 4 to 8 weeks after resection is associated with better overall survival than an RT delay of >8 weeks for patients with newly diagnosed glioblastoma.

The optimal timing of RT from surgery before this 8-week cutoff is unknown, particularly in elderly patients with glioblastoma. Adeberg et al¹⁸ investigated favorable glioblastoma patients and demonstrated initiating RT sooner than 24 days after surgery has a negative impact on progression and survival. This is contrary to our findings demonstrating initiation of RT $\leq$ 20 days from date of surgery demonstrated improved OS. This discrepancy could be due to the authors investigating a favorable patient cohort with a median KPS of 90 who were optimal candidates for systemic therapy as opposed to our elderly patient cohort with a median KPS of 70.

Elderly patients with poorer performance status with newly diagnosed glioblastoma are often times suboptimal candidates for adjuvant temozolomide after RT.¹⁹ Our elderly patient cohort had only 26 patients (46%) receiving adjuvant chemotherapy, underscoring the impact of early initiation of RT in a patient population who are not uniformly receiving systemic therapy. Furthermore, our previous work demonstrated that high or low performance status in elderly patients with glioblastoma multiforme (GBM) did not affect patient outcomes in this population regardless of RT fractionation.²⁰ This study emphasizes the need to tailor adjuvant therapy on a case-by-case basis to maximize patient outcomes. Our work underscores the survival benefits of initiating treatment with chemotherapy in addition to RT in elderly patients with GBM, demonstrated by Perry et al.²¹

Previous literature has demonstrated that aggressive management with surgical resection should be considered in elderly patients with glioblastoma, even those with relatively poor performance status.²² Perioperative complications in elderly patients and surgically acquired neurological deficits could affect patients' inpatient rehabilitation progress and recover.²³ Our results highlight that potential delays to initiation of RT could affect survival outcomes in elderly patients with glioblastoma. Furthermore, our results demonstrate that these improved survival outcomes are observed after adjustment for multiple prognostic variables.

Limitations

Our multivariate analysis demonstrates that the impact of early RT in elderly patients with GBM is not independent of other clinical factors. The lack of significant main or interaction effects suggests that the observed difference in univariate analysis is confounded by other clinical variables, including performance status and adjuvant therapy. Elderly patients with GBM who are poor performers are particularly affected by the logistics of daily RT which both conventionally and hypofractionated RT regimens require.²⁴ We postulate that these bedridden and dependent elderly GBM patients have functional limitations which potentially delayed their initiation to RT.

We summarized the experiences of our practice regarding timing of RT from surgery in elderly patients diagnosed with GBM. Our outcomes are prone to bias, particularly regarding our patient population treatment experiences and the retrospective nature of this study. Regardless, our treatment decision making and management approach is reflective of challenges encountered nationwide by practitioners and is highly relevant to neurosurgery and neuro-oncology.

CONCLUSION

Early initiation of RT in elderly patients with newly diagnosed glioblastoma improves both overall survival and progression-free survival. The significant positive association between early initiation of RT and survival outcomes was retained after accounting for potential confounding factors. Timing of RT is particularly of significance in this patient population who may not be optimal candidates for systemic chemotherapy. Our as-yet-unpublished experience of survival outcomes across glioblastoma in all age groups will shed further insight on the impact of timing of RT from surgery. A prospective randomized trial designed to evaluate the impact of timing of RT or concurrent chemoradiation is paramount to optimize outcomes in this vulnerable patient population.

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The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Supplemental Digital Content 1. Analysis of Impact of Performance Status on OS in the early/late RT group.

Supplemental Digital Content 2. Analysis of Impact of Adjuvant Temozolomide on OS in the early/late RT group.

Supplemental Digital Content 3. Analysis of Impact of Tumor Volume on OS in the early/late RT group.

Supplemental Digital Content 4. Analysis of Impact of Brainstem/Basal Ganglia Involvement on OS in the early/late RT group.

Supplemental Digital Content 5. Subgroup Analysis of Preoperative Midline Shift on OS in the early/late RT group.

Supplemental Digital Content 6. Subgroup Analysis of Postoperative Midline Shift on OS in the early/late RT group.

Supplemental Digital Content 7. Subgroup Analysis of Preoperative edema on OS in the early/late RT group.

Supplemental Digital Content 8. Subgroup Analysis of Postoperative edema on OS in the early/late RT group.

Supplemental Digital Content 9. Subgroup Analysis of Bilateral Involvement on OS in the early/late RT group.

Supplemental Digital Content 10. Subgroup Analysis of MGMT status on OS in the early/late RT group.

Supplemental Digital Content 11. Subgroup Analysis of Tumor volume on OS in the early/late RT group.

COMMENTS

Treatment of glioblastoma remains challenging as neurosurgeons, neuro-oncologists, and radiation oncologists strive to improve outcomes in a multidisciplinary fashion. One critical decision point is the timing of radiation, especially in elderly patients (>65 years). Currently, the literature supports that initiation of radiation about 4 to 8 weeks postoperatively leads to better overall survival and delaying beyond 8 weeks leads to worse outcomes. The optimal timepoint within the 4 to 8 week range has not been determined.^{1a-8a} This provides the authors the necessary clinical equipoise to investigate the impact of initiating early radiation in elderly patients with newly diagnosed GBM.

On univariate analysis, the authors found that patients who received early radiation (<20 days postoperative) had significantly higher overall and progression-free survival. However, on multivariate analysis this trend was not appreciated, implying presence of confounding factors such as need for rehab, low KPS, prolonged hospitalization some of which may also be associated with decreased survival. An important point underscored in this manuscript is that, even in elderly patients, timely initiation of adjuvant therapies is key. Univariate and multivariate analysis showed adjuvant temozolomide significantly improved progression-free survival. The authors do not evaluate differences in complication rates, particularly wound dehiscence or surgical site infections which would be of concern with early initiation of radiation.

Despite the results of the multivariate analysis, this paper adds to the scholarly dialogue of best treatment practices in elderly patients and demonstrates the need for continued investigation. Care of the individual patient must be individualized based on their performance status, comorbidities, and patient wishes.

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