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Postoperative glioblastoma: the effect of radiotherapy timing on prognosis

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Abstract

Objectives: To evaluate the prognostic impact of the interval between surgery and the initiation of postoperative radiotherapy (RT) in patients with glioblastoma (GB).

Methods: This retrospective cohort study included patients diagnosed with GB and treated with surgical resection followed by adjuvant RT at a single institution between 21 April 21 and 20 December 2022. Patients were grouped according to the time interval between surgery and RT initiation (≤4, 4–6 and >6 weeks). Most patients received 60 Gy in 30 fractions; elderly or low-performance patients received 40.05 Gy in 15 fractions. Survival outcomes, including overall survival (OS) and progression-free survival (PFS), were assessed. Kaplan–Meier survival analysis and Cox proportional hazards modelling were performed.

Results: 132 patients were included. Median time from surgery to RT initiation was 32 days. Patients who began RT within 4–6 weeks had better OS and PFS compared to those treated earlier or later. On multivariate analysis, initiating RT after more than 6 weeks was associated with worse OS (HR: 1.72, 95% CI: 1.12–2.63, $p = 0.013$). Initiation within 3 weeks trended toward inferior outcomes, though not statistically significant. RT dose distribution: ~85% received 60 Gy/30 fr, and ~15% received 40.05 Gy/15 fr.

Conclusion: Timing of postoperative RT significantly impacts survival outcomes in GB patients. Initiating treatment between 4 and 6 weeks post-surgery may provide optimal benefit. These findings support careful planning of adjuvant RT to avoid undue delay or premature initiation.

Keywords: *glioblastoma*, *radiotherapy*, *timing*, *postoperative care*, *overall survival*, *progression-free survival*

Research

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Introduction

Glioblastoma (GB) is the most aggressive primary brain tumour, characterized by a dismal prognosis despite advancements in surgery, radiotherapy (RT) and chemotherapy. The current standard of care involves maximal safe resection followed by concurrent chemoradiotherapy and adjuvant temozolomide (TMZ). The optimal timing of postoperative RT remains an unresolved and clinically relevant issue in GB management. Literature highlights that both delays and premature initiation of RT can influence survival outcomes.

Several studies have addressed this topic, though with conflicting results. Katsigiannis *et al* [1] demonstrated that delays in RT initiation adversely affect survival, while Buszek *et al* [2] emphasized timely RT following gross total or subtotal resection (STR). Conversely, Zhang *et al* [3] and Zur Mühlen *et al* [4] suggested that early RT initiation may negatively impact prognosis due to incomplete surgical recovery. Blakstad *et al* [5] and Magrowski *et al* [6] further underscore the complexity of defining an optimal RT window, influenced by patient-specific and institutional factors. Earlier evidence from Lawrence *et al* [7] and Do *et al* [8] indicated that both excessive delays and very short intervals could worsen outcomes. More recent observational studies have further explored these conflicting findings, without reaching a clear consensus regarding the optimal timing of RT initiation [9–11,13]. The pivotal trial by Stupp *et al* [12] established the survival benefit of combining RT with concurrent and adjuvant TMZ. Within this therapeutic framework, the present study evaluates the effect of postoperative RT timing on survival outcomes in patients with GB in a real-world clinical setting.

Materials and methods

Study design and setting

This retrospective cohort study included GB patients treated with postoperative RT at three tertiary care centres in Ankara, Turkey, between 21 April 2015 and 20 December 2022. It was approved by Ankara City Hospital Ethics Committee (E1-23-3223) and conducted according to the Declaration of Helsinki.

Patient selection

Inclusion criteria:

1. Histopathological confirmation of GB.
2. Age ≥18 years.
3. Completion of postoperative RT with or without concurrent chemotherapy.

Exclusion criteria:

- Diffuse gliomas, gliosarcomas, incomplete follow-up or palliative treatment Palliative RT was defined as <45 Gy or short-course hypofractionated RT applied solely for symptom palliation. Eight patients were excluded for non-GB histology.

Radiotherapy

- The majority of patients received 60 Gy in 30 fractions.
- Elderly or low-performance patients received 40.05 Gy in 15 fractions.

Performance status

All patients had a baseline Karnofsky Performance Status corresponding to ECOG 0–2.

Concurrent and adjuvant TMZ

Concurrent TMZ was administered at a dose of 75 mg/m²/day orally, daily throughout the entire course of RT. All patients subsequently received adjuvant TMZ for a planned total of six cycles, according to standard treatment protocols.

Follow-up imaging protocol

Follow-up evaluation was performed using contrast-enhanced magnetic resonance imaging, including diffusion-weighted imaging and perfusion-weighted imaging, at regular intervals during post-treatment surveillance.

Follow-up

The median follow-up was 24.5 months (IQR 18.2–30.7). Patients were followed every 3 months for 2 years, then every 6 months until death or censoring.

Outcomes

- Overall survival (OS): from surgery to death/last follow-up.
- Progression-free survival (PFS): from surgery to progression/last follow-up without progression.

Statistical analysis

Kaplan–Meier method and Cox proportional hazards regression (SPSS v26) were used. p <0.05 considered significant. Sensitivity analyses excluded patients with very early RT (14–21 days), prolonged RT delay (≥43 days) or <12 months follow-up.

Results

Patient characteristics

A total of 132 patients were included in the study. The median age was 61 years (range: 23–79), with 42 (39.4%) females and 80 (60.6%) males. Gross total resection (GTR) was achieved in 16 patients (12.1%), while 116 patients (87.9%) underwent STR. All patients received postoperative RT, with the majority treated using the standard schedule of 60 Gy in 30 fractions (n = 112, 85%), while older or frail patients received hypofractionated RT of 40.05 Gy in 15 fractions (2.67 Gy × 15 fr, n = 20, 15%). Concurrent TMZ chemotherapy was administered in 111 patients (84.1%). All patients who received TMZ completed the planned concurrent and adjuvant treatment without dose reduction or interruption. The median number of adjuvant TMZ cycles was six. The low GTR rate and incomplete TMZ coverage reflect real-world factors including advanced age, comorbidities, tumour location and logistical or social limitations.

Follow-up

The median follow-up time was 24.5 months (IQR: 18.2–30.7). Patients were followed at 3-month intervals during the first 2 years post-RT and at 6-month intervals thereafter until death or censoring.

RT schedules

Postoperative RT was delivered using standard fractionation for the majority of patients (60 Gy in 30 fractions, 2 Gy per fraction, n = 112, 85%) and hypofractionated schedules for elderly or frail patients (40.05 Gy in 15 fractions, 2.67 Gy per fraction, n = 20, 15%). Palliative RT, defined as <45 Gy or short-course RT for symptomatic relief, was applied in excluded cases and is not represented in the final cohort.

Timing of RT initiation

Patients were grouped according to the interval from surgery to RT initiation. RT delay was defined as the interval between surgery and initiation of postoperative RT.

- 14–21 days: 4 patients (3.0%)
- 22–28 days: 15 patients (11.4%)
- 29–42 days: 73 patients (55.3%)
- ≥43 days: 40 patients (30.3%)

The median interval from surgery to RT initiation from 32 days to 37 days (range: 14–150). RT timing was additionally categorized according to deviations from the planned postoperative treatment schedule. RT was initiated within the planned postoperative interval in 93 patients (70.5%), while delays of ≤2, 2–4 and >4 weeks were observed in 29 (22.0%), 5 (3.8%) and 5 patients (3.8%), respectively.

Survival outcomes

Patients were grouped according to the interval between surgery and RT initiation: 14–21 days (n = 4), 22–28 days (n = 15), 29–42 days (n = 73) and ≥43 days (n = 40). RT delays were further categorized: no delay in 93 patients (70.5%), a delay of ≤2 weeks in 29 patients (22.0%), 2–4 weeks in 5 patients (3.8%) and >4 weeks in 5 patients (3.8%). The definition of palliative RT included doses <45 Gy or RT delivered solely for symptom palliation.

Median OS differed across RT timing groups:

- 14–21 days: OS ranged between 3 and 11 months, and all patients in this group were deceased at final follow-up.
- 22–28 days: median OS 19 months (range: 10–51)
- 29–42 days: median OS 16 months (range: 3–66), with five patients still alive at last follow-up (6.8%).
- ≥43 days: median OS 13 months (range: 3–49), two patients alive (5.0%)

Kaplan–Meier analysis demonstrated a clinically meaningful trend favouring RT initiation between 22 and 28 days post-surgery, though the differences did not reach statistical significance (p = 0.057) (Figure 1).

PFS differed among RT timing groups as follows: 14–21 days: median PFS 6 months (range: 1–9); 22–28 days: 12 months (range: 1–18); 29–42 days: 8 months (range: 1–51); ≥43 days: 13 months (range: 3–49).

PFS did not differ significantly among groups (p = 0.39) (Figure 2).

Acute toxicity and recurrence management

Acute toxicities during RT, including nausea, vomiting and fatigue, were observed in 39 patients (29.5%). Severe toxicity requiring hospitalisation occurred in nine patients (6.8%).

Recurrence management included:

- Reoperation: 21 patients (15.9%)
- Re-irradiation: 18 patients (13.6%), with doses ranging from 21 Gy/3 fractions to 35 Gy/10 fractions
- Chemotherapy: 12 patients (9.1%)

At final follow-up, 7 patients (5.3%) were alive, and 125 (94.7%) had died.

Table 1 summarizes patient characteristics, RT timing groups and survival outcomes.

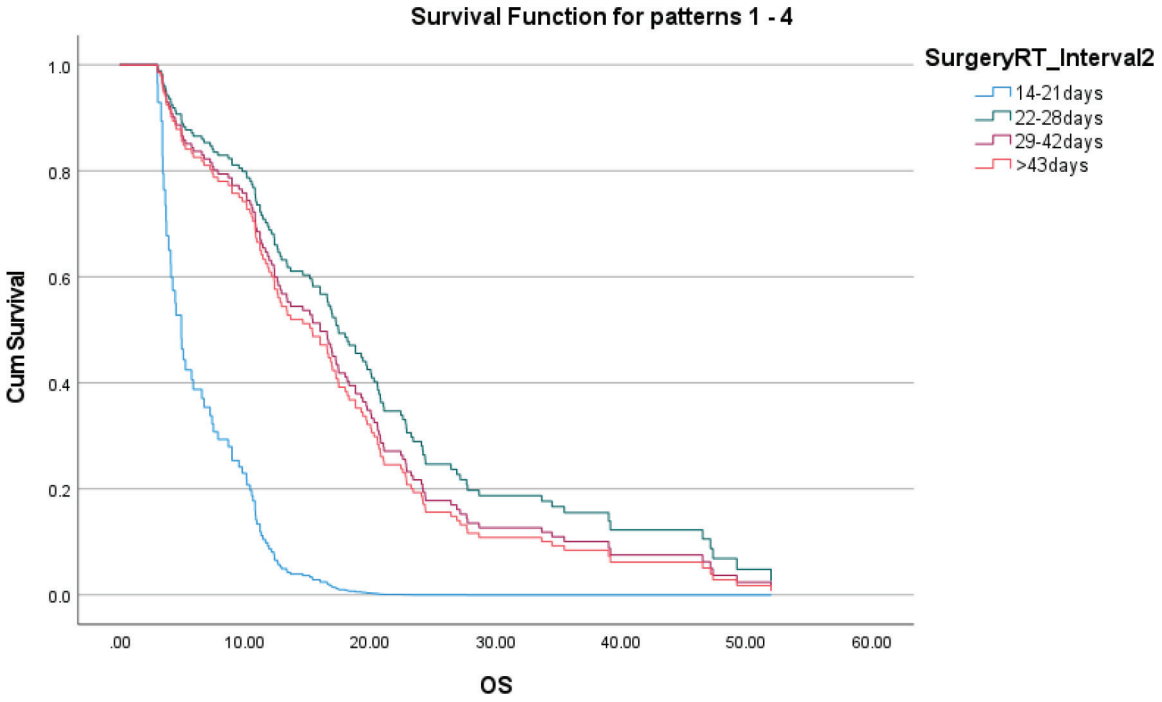

Figure 1. Kaplan–Meier OS curves stratified by time interval between surgery and RT initiation.

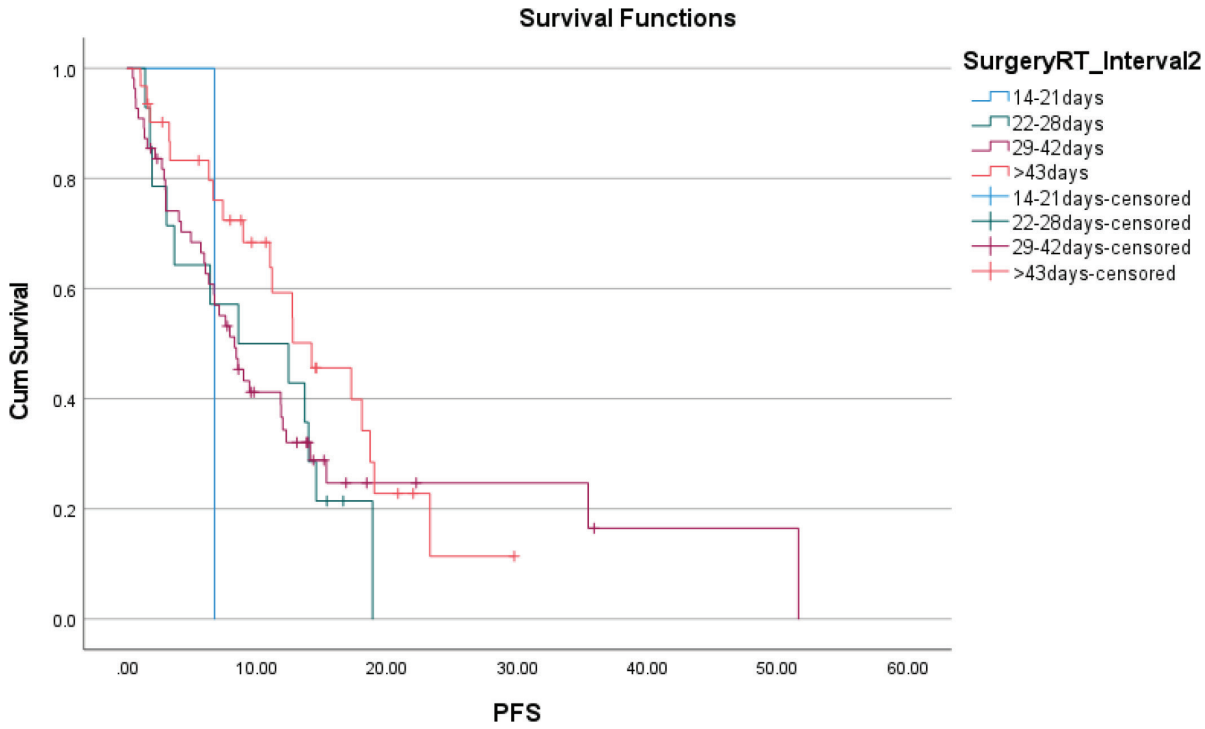

Figure 2. Kaplan–Meier curves illustrating the relationship between PFS and timing of postoperative RT initiation.

Table 1. Patient characteristics and survival outcomes according to surgery–RT interval.

RT interval (days)	*N* (%):	Median OS † (months, range	Median PFS ‡ (months, range):	Alive, *n* (%)	RT Dose (*n*, %)	GTR *n* (%)
14–21	4 (3.0)	3–11	1–9	0 (0%)	60 Gy/30 fr, 4 (100%)	0 (0%)
22–28	15 (11.4)	19 (10–51)	12 (1–18)	0 (0%)	60 Gy/30 fr, 12 (80%), 40.05 Gy/15 fr, 3 (20%)	2 (13.3%)
29–42	73 (55.3)	16 (3–66)	8 (1–51)	5 (6.8%)	60 Gy/30 fr, 62 (84.9%), 40.05 Gy/15 fr, 11 (15.1%)	9 (12.3%)
≥43 days	40 (30.3)	13 (3–49)	13 (3–49)	2 (5.0%)	60 Gy/30 fr, 34 (85%), 40.05 Gy/15 fr, 6 (15%)	5 (12.5%)
Total	132 (100)			7 (5.3%)	60 Gy/30 fr, 112 (85%), 40.05 Gy/15 fr, 20 (15%)	16 (12.1%)

Abbreviations: OS †: overall survival; PFS ‡: progression-free survival

Discussion

The timing of postoperative RT in GB remains a central yet unresolved issue in neuro-oncology. Our study reinforces existing evidence that both excessively early and delayed initiation of RT may negatively affect survival outcomes.

Patients receiving RT within 14–21 days post-surgery demonstrated the poorest median OS, ranging from 3 to 11 months. Although this subgroup was small ($n = 4$), the trend aligns with previous studies suggesting that early RT may exacerbate postoperative inflammation, impair wound healing or limit the efficacy of adjuvant therapy [4]. Rapid initiation may also interfere with the resolution of peritumoral oedema and the recovery of surrounding brain tissue, potentially compromising radiation tolerance and increasing toxicity risk.

Delays beyond 43 days were associated with a trend toward decreased OS, consistent with prior reports [1, 2, 5, 6, 11]. Tumour repopulation and disease progression during prolonged intervals may reduce the therapeutic benefit of RT. These findings highlight a critical 'therapeutic window', emphasising that both premature and delayed RT can adversely affect outcomes.

In our cohort, the optimal window for RT initiation appears to be between 22 and 42 days post-surgery. The highest median OS (19 months) was observed in the 22–28 day group, whereas the largest cohort (29–42 days) had a median OS of 16 months. This window likely balances adequate postoperative recovery with the urgency of adjuvant therapy, allowing tissues to heal sufficiently while minimising tumour progression.

Most patients (85%) received standard fractionation (60 Gy in 30 fractions). Hypofractionated RT (40.05 Gy in 15 fractions, 2.67 Gy per fraction) was applied to elderly or frail patients, reflecting individualized clinical decisions. Hypofractionation is increasingly used in patients with poor performance status or significant comorbidities, providing effective local control with fewer hospital visits [10]. Including both standard and hypofractionated schedules ensures our findings reflect real-world practice.

Concurrent TMZ was administered in 84.1% of patients. While TMZ can modulate tumour proliferation during RT waiting periods, the relatively low coverage reflects real-world constraints such as patient age, comorbidities or logistical issues affecting treatment adherence. The interplay between TMZ administration and RT timing underscores the importance of integrating systemic therapy planning with radiation scheduling to optimize outcomes.

The GTR rate in our cohort was 12.1%, considerably lower than the 60%–80% reported in clinical trials. This discrepancy reflects routine clinical practice, where patient age, tumour location, surgical feasibility and social or logistical limitations often prevent maximal resection. The predominance of STRs further highlights the challenges of translating trial outcomes to broader clinical settings.

A major limitation is the lack of molecular profiling, including O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, isocitrate dehydrogenase (IDH) mutation and epidermal growth factor receptor amplification. These biomarkers are known to influence prognosis, treatment response and survival [12]. The absence of these data limits the ability to stratify patients based on tumour biology. However, archived tumour material could be analysed in future prospective studies to enable molecularly guided subanalyses, thereby improving the interpretability and generalisability of RT timing effects.

Our findings are broadly consistent with prior retrospective and observational studies [1–11]. While some studies suggest early RT may be beneficial, others demonstrate that very short intervals can be detrimental due to unresolved postoperative inflammation or surgical recovery issues. Conversely, prolonged delays consistently correlate with worse survival. By including both standard and hypofractionated RT schedules and real-world patient populations, our study complements existing literature by providing practical, clinically relevant insights. Survival outcomes may also have been influenced by confounding factors such as patient age, performance status, extent of resection and unavailable molecular markers, rather than RT timing alone.

These results emphasize the importance of careful multidisciplinary coordination in the postoperative management of GB patients. Initiation of RT between 3 and 6 weeks after surgery appears to provide a balance between adequate postoperative recovery and timely initiation of adjuvant treatment, potentially optimising survival outcomes. Delays in RT may arise from a combination of system-related factors (treatment planning capacity and scheduling constraints), patient-related factors (postoperative recovery, comorbidities and referral delays) and workflow-related factors (imaging availability and multidisciplinary decision-making processes). Early involvement of radiation oncology in the postoperative period, improved multidisciplinary communication, optimized scheduling systems and prioritisation pathways for high-grade glioma patients may help reduce unnecessary delays in treatment initiation.

Limitations and future directions

This study is limited by its retrospective design, modest sample size, group size imbalance and lack of molecular data. The small number of patients in the earliest RT group (14–21 days) limits the statistical power to draw definitive conclusions regarding premature initiation. In addition, the absence of molecular profiling (including MGMT, IDH and other relevant biomarkers) further restricts patient stratification and limits biological interpretation of survival differences. Furthermore, multivariate analysis was not performed due to the retrospective design and the primarily descriptive nature of the study, which limits adjustment for potential confounding factors. Future prospective studies incorporating molecular markers, patient-reported outcomes and standardized RT protocols are needed to refine the optimal timing of postoperative RT and provide individualized recommendations.

Conclusion

Our single-centre retrospective analysis indicates that initiating postoperative RT between 3 and 6 weeks after surgery is associated with improved OS in GB patients. Both early (≤3 weeks) and delayed (≥6 weeks) RT initiation were linked to worse outcomes. Standard fractionation (60 Gy/30 fractions) was feasible for most patients, while hypofractionated RT (40.05 Gy/15 fractions was a safe alternative for selected elderly or frail patients. These findings highlight the importance of careful multidisciplinary planning of RT timing in routine clinical practice.

Conflicts of interest

The authors declare no conflicts of interest.

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References

1. Katsigiannis S, Rapp M, and Reifenberger G, *et al* (2019) **Influence of delay in radiotherapy on survival in patients with glioblastoma** *Radiother Oncol* **134** 103–110
2. Buszek SM, Michael NM, and Yan E, *et al* (2020) **A systematic review of the impact of the time interval from surgery to the start of concurrent chemoradiotherapy in glioblastoma patients** *J Neurooncol* **148** 1–9
3. Zhang Y, Fang L, and Sun H, *et al* (2020) **Impact of early versus delayed postoperative radiotherapy on the prognosis of glioblastoma: a retrospective study** *Clin Neurol Neurosurg* **196** 106019
4. Zur Mühlen R, Eisenmann C, and Simon M, *et al* (2020) **Timing of radiotherapy following resection of glioblastoma: an analysis of the impact on survival** *J Neurooncol* **146** 591–599
5. Blakstad O, Solheim O, and Scheie D, *et al* (2020) **Delayed initiation of radiotherapy in glioblastoma patients: impact on survival and progression-free survival** *Acta Neurochir (Wien)* **162** 2777–2785
6. Magrowski P, Tarnawski R, and Miszczyk M (2020) **Optimal timing of postoperative radiotherapy for glioblastoma patients—a single institution experience** *Rep Pract Oncol Radiother* **25** 893–899
7. Lawrence YR, Blumenthal DT, and Matceyevsky D, *et al* (2011) **Delayed initiation of radiotherapy in glioblastoma patients: a retrospective study** *Int J Radiat Oncol Biol Phys* **81** 375–381
8. Do V, Gebski V, and Barton MB (2000) **The effect of waiting for radiotherapy for grade III/IV gliomas** *Radiother Oncol* **57** 131–136 https://doi.org/10.1016/S0167-8140(00)00257-7 PMID: 11054516
9. Wang Y, Chen L, and Bao J, *et al* (2016) **Effects of delay in radiotherapy on survival in patients with glioblastoma** *Radiother Oncol* **120** 219–223
10. Blumenthal DT, Won M, and Mehta MP, *et al* (2018) **Short delays in radiation therapy do not impact survival of glioblastoma patients enrolled onto RTOG 0525** *Int J Radiat Oncol Biol Phys* **101** 1146–1153
11. Seidlitz A, Siepmann T, and Lotsch D, *et al* (2015) **Impact of radiotherapy delay in glioblastoma: a multi-institutional observational study** *Strahlenther Onkol* **191** 149–154
12. Stupp R, Mason WP, and van den Bent MJ, *et al* (2005) **Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma** *N Engl J Med* **352** 987–996 https://doi.org/10.1056/NEJMoa043330 PMID: 15758009
13. Ahn S, Park JS, and Lee JH, *et al* (2020) **Institutional factors affecting delays in postoperative radiotherapy for glioblastoma** *Radiat Oncol J* **38** 179–185