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Optimal timing of chemoradiation after resection or biopsy of glioblastomas: a nationwide population-based study

Dongeun Lee[1,2,3†], Eunyoung Lee[4†], Tae Hoon Roh[1*] and Se-Hyuk Kim[1]

Abstract

Background This study investigated the optimal timing of concurrent chemoradiotherapy (CCRT) following surgery for patients with newly diagnosed glioblastoma (GBM). The focus was on understanding whether the interval between surgery and CCRT impacts survival outcomes.

Methods Data from the Korean National Health Insurance Research Database (https://opendata.hira.or.kr/) were collected to retrospectively review 3,586 patients diagnosed with GBM in South Korea between 2008 and 2021. Patients were divided into early CCRT (≤ 21 days between surgery and CCRT) and late CCRT (> 21 days between surgery and CCRT) groups and further categorised based on the type of surgery (biopsy alone or surgical resection). The study estimated overall survival (OS) and conducted univariable and multivariable Cox regression analyses.

Results The median overall survival (OS) for the entire cohort was 19.98 months (95% Confidence Interval [CI]: 19.12–20.86 months). In univariable analysis, the late CCRT group demonstrated a longer median OS compared to the early CCRT group (20.47 vs. 17.94 months, $P=0.0002$, log-rank test). However, this difference was not significant in multivariable analysis (Hazard Ratio [HR] = 0.98, 95% CI: 0.782–1.091, $P=0.6663$). Subgroup analysis revealed that late CCRT was associated with prolonged OS in patients who underwent surgical resection (adjusted HR = 0.85, 95% CI: 0.752–0.955, $P=0.0065$), whereas in the biopsy-alone group, late CCRT was associated with shorter OS (adjusted HR = 1.80, 95% CI: 1.378–2.346, $P<0.0001$).

Conclusions Patients who initiated CCRT more than 21 days post-resection demonstrated improved overall survival (OS) compared to those who began CCRT earlier. In contrast, among patients who underwent biopsy alone, initiating CCRT within 21 days was associated with better outcomes. These findings suggest that the optimal timing for CCRT initiation in GBM may depend on the extent of residual tumour.

Keywords Chemoradiation, Surgery, Biopsy, Glioblastomas, Optimal timing

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Background

Glioblastoma (GBM), the most prevalent primary brain tumour in adults, presents a formidable treatment challenge because of its aggressive nature and dismal prognosis, with an average overall survival (OS) of approximately 15 months [1, 2]. The current standard of care involves maximal safe surgical resection of the tumour, followed by concurrent chemoradiotherapy (CCRT) with temozolomide (TMZ) chemotherapy, typically administered within a 6-week postoperative window [3–6]. This regimen is based on evidence of significantly poorer survival outcomes with radiotherapy (RT) initiation more than 6 weeks postoperatively [7].

Despite the urgency in commencing CCRT to combat tumour regrowth, the timeline for initiating postoperative CCRT remains a subject of medical debate. Pathological confirmation of GBM can take more than 2 weeks, and additional time may be required for molecular studies such as IDH mutation and MGMT promoter methylation analysis, which are essential components of the latest diagnostic standards [8]. Consequently, the timing of CCRT initiation varies considerably.

Contradictory findings have been reported on the optimal timeframe for starting RT, with some suggesting that delayed RT correlates with extended OS [9–16], whereas others advocate for earlier RT for better survival outcomes [4, 17, 18]. Furthermore, other studies indicated no significant correlation between the timing of postoperative RT and OS [19–27].

This study aimed to elucidate the optimal interval for initiating postoperative CCRT in patients with GBM by using comprehensive data from a nationwide, population-based database. By examining a large cohort, we intended to provide clearer guidance on this crucial aspect of GBM treatment, which has clinical implications for patient outcomes and treatment planning.

Methods

Study design and population

The study protocol adhered to the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 1983, and was approved by the Institutional Review Board of Ajou University Hospital (approval number: AJOUIRB-EX-2022-314). As this study utilized previously collected data from the National Health Insurance claims database, the requirement for informed consent was waived. The patient data included in this study were collected from the Korean Health Insurance Review and Assessment Service (HIRA) database (https://opendata.hira.or.kr/). The HIRA service is provided by the government and manages the quality standards of medical services by reviewing all health claims in Korea, covering 97.1% of the whole population. By leveraging the HIRA database, we retrospectively reviewed patients with newly diagnosed GBM treated with standard adjuvant CCRT. The eligibility criteria included the following: newly diagnosed patients with C71.x code (GBM diagnostic code) according to the International Classification of Diseases, 10th revision (ICD-10) coding system [28] and those who had been treated with craniotomy for surgical resection (S4634, S4635, S4636, and S4637) or biopsy (S4756) followed by adjuvant RT (HD061, HZ271) and TMZ (358202ACH, 358203ACH, 358204ACH) between 2008 and 2021. Patients who underwent either radiotherapy or chemotherapy alone were excluded from the study. In total, 8,738 patients were included.

Given the characteristics of the claims data and the robustness of estimating the start date of RT compared with the start date of TMZ chemotherapy, our study adopted the assumption that the initiation of RT also marked the commencement of CCRT TMZ may be prescribed in advance but CCRT typically begins with RT, making the RT start date from the EDI code more accurate. This approach was necessitated by the challenge in accurately determining the onset of chemotherapy due to the timing of prescription claims. Therefore, in instances where the prescription date for TMZ and the start date for RT differed, the start date of RT was considered the initiation date of CCRT. This assumption allows for a more definitive analysis of treatment initiation within the constraints of the available data.

The Korean health insurance system follows a fee-for-service model, with RT having distinct charges for treatment planning and irradiation. Treatment planning, which precedes actual treatment, was assessed through the prescription codes for three-dimensional conformal RT (HD061) and intensity-modulated RT (HZ271). The index date for each participant was determined by the later of either the biopsy alone or tumour resection date. The interval between surgery and RT initiation was calculated by subtracting the index date from the RT start date (HD061 and HZ271). Patients who commenced chemotherapy (as confirmed by TMZ prescription status) > 20 days after starting RT were excluded. Additionally, patients receiving RT > 6 weeks postoperatively were excluded, aligning with the Stupp protocol, which constitutes the standard of care for GBM treatment [1, 3].

Patients with a ≥ 90-day interval between the first diagnosis (C71.x code) and surgery ($n = 284$) were excluded to minimise the variables of recurrence and re-diagnosis after a primary diagnosis of non-GBM. Patients aged < 18 years at first diagnosis ($n = 79$) were excluded, as gliomas that occur in this age group are likely to exhibit different characteristics than those in adults. Those who died within 90 days after surgery ($n = 105$), had received short-course radiation (RT < 15 days in total, $n = 780$),

underwent a biopsy after tumour resection ($n=32$), and whose exact date of RT initiation could not be estimated (owing to the nature of insurance claims data, the surgery and RT fee are usually claimed on the same date among hospitalised patients, $n=1,042$) were excluded.

Among the final study population of 3,586, patients who received CCRT ≤ 21 days after surgery were defined as the early CCRT group ($n=567$), and those who received 21 < CCRT ≤ 42 days were defined as the late CCRT group ($n=3,019$) (Fig. 1). The endpoint was OS, which was defined as the length of time from operation to death or the last date of survival confirmation. As Korean health insurance system which all Korean citizens are automatically enrolled follows a fee-for-service model, for patients without health insurance claims for > 6 months, the last claims date was considered the date of death. The follow-up time was defined as the period from the initial treatment to either the last claim date for each patient or the end of the study period, whichever came first, to ensure consistency across the cohort.

Covariables

Details of the participants' characteristics were obtained from the database. Covariables included sex, age, procedure type (biopsy alone or tumour resection), comorbidities (hypertension [HTN] and diabetes mellitus [DM]), interval between diagnosis and operation, hospital admission status at CCRT initiation, length of hospitalisation within 90 days after surgery (including a tertiary hospital), and number of adjuvant TMZ cycles.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences software (IBM Corp., Armonk, NY, USA). The OS rate was determined using the Kaplan–Meier survival model, and the risk of occurrence was identified using the Cox proportional hazards regression model by calculating the hazard ratio (HR) and 95% confidence interval (CI). Univariable and multivariable covariables were analysed separately using Cox proportional hazards analyses. A pairwise comparison was performed using the log-rank test between weeks after RT initiation. A P-value of < 0.05 was considered the threshold for significance.

Results

Patient characteristics

A total of 3,586 patients met the inclusion criteria and were enrolled in this study. The baseline characteristics of the patients are presented in Table 1. The mean

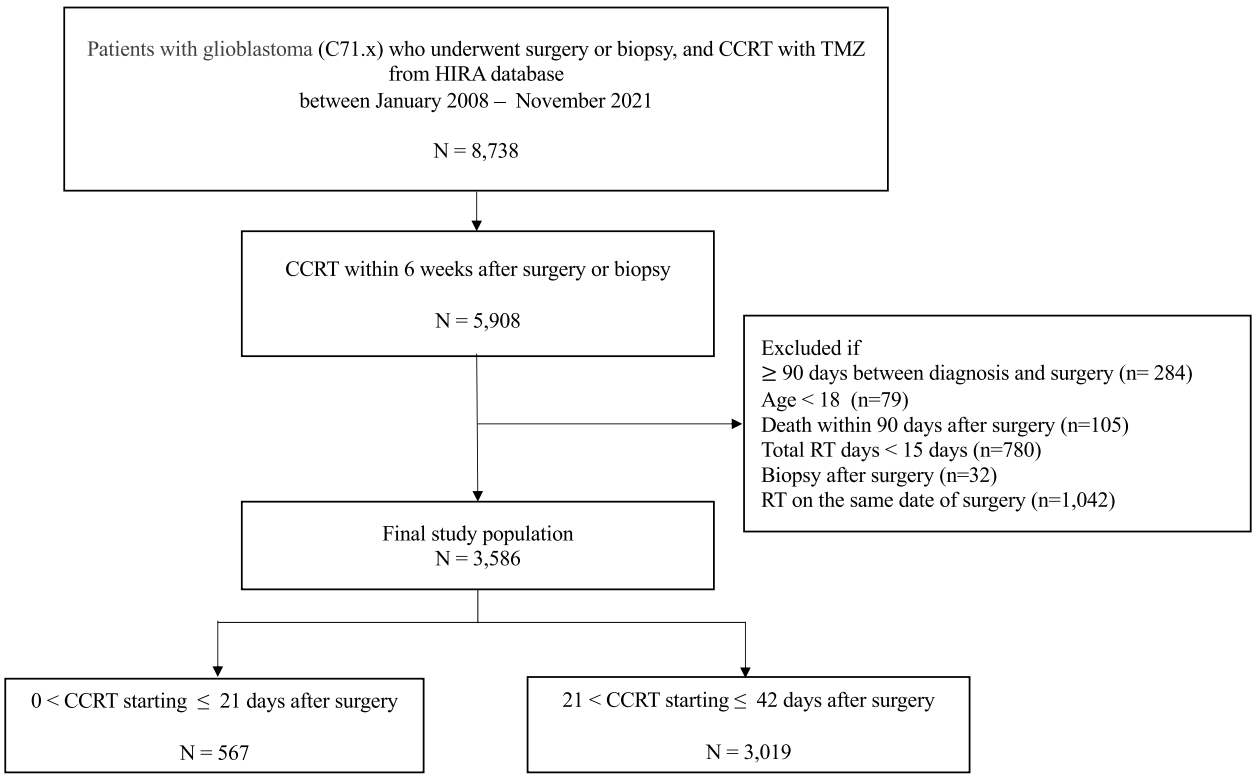

Fig. 1 Flow diagram for selection of patients in this study. CCRT: concurrent chemoradiotherapy; TMZ: temozolomide; HIRA: Health Insurance Review and Assessment Service; RT: radiotherapy

Table 1 Population characteristics

	All $N=3,586$	Early CCRT (≤ 21 days) $N=567$	Late CCRT (> 21 days) $N=3,019$	*P*
Sex, n (%)				0.6148
Male	2,033 (56.69)	316 (55.73)	1,717 (56.87)	
Female	1,553 (43.31)	251 (44.27)	1,302 (43.13)	
Age, years, mean ± SD	57.35 ± 12.68	56.92 ± 13.04	57.43 ± 12.61	0.3854
The procedure, n (%)				< .0001
Tumour resection	3,289 (91.72)	442 (77.95)	2,847 (94.30)	
Biopsy alone	297 (8.28)	125 (22.05)	172 (5.70)	
Hypertension, n (%)	1,268(35.36)	179 (31.57)	1,089 (36.07)	0.0397
Diabetes mellitus, n (%)	582 (16.23)	73 (12.87)	509 (16.86)	0.0182
Time to surgery, days from diagnosis, median [IQR]	3 [0, 12]	3 [0, 9]	4 [0, 10]	0.1600
Patient status during radiotherapy				< .0001
Inpatient	876 (24.43)	271 (47.80)	605 (20.04)	
Outpatient	2,710 (75.57)	296 (52.20)	2,414 (79.96)	
Duration of hospitalisation within 90 days after surgery, days, median [IQR]				
Tertiary hospital only	15 [10, 24]	17 [11, 47]	14 [10, 22]	< .0001
All hospitals	19 [12, 46]	30 [13, 63]	18 [12, 39]	< .0001
Number of adjuvant TMZ cycles				
mean ± SD	4.68 ± 1.75	4.51 ± 1.72	4.71 ± 1.75	0.0233
< 3	504 (16.14)	85 (18.64)	419 (15.72)	0.1375
3–6	2,551 (81.71)	358 (78.51)	2193 (82.26)	
> 6	67 (2.15)	13 (2.85)	54 (2.03)	

CCRT concurrent chemoradiotherapy, *IQR* interquartile range, *RT* radiation therapy, *SD* standard deviation, *TMZ* temozolomide

age of the patients was 57.4 ± 12.7 years, and 56.7% were male ($n=2,033$). Most of the patients underwent surgery (91.72%, $n=3,289$) and received CCRT in outpatient settings (75.57%, $n=2,710$). Comparison of the baseline patient characteristics between the early and late CCRT groups revealed significant intergroup differences in comorbidities (both HTN and DM), procedure type, admission status for CCRT, duration of hospitalisation, and mean number of adjuvant TMZ cycles.

Overall survival analysis

With the reverse Kaplan–Meier method, the median follow-up period was 48.69 (95% CI, 45.24–53.75) months. The median OS period for the entire cohort was 19.98 (95% CI, 19.12–20.86) months (Fig. 2a) in the entire cohort. Univariable analysis demonstrated that delayed initiation of CCRT more than 21 days after tumour resection was associated with longer OS ($P=0.0002$); however, this association was not statistically significant in multivariable analysis ($P=0.6663$). At the time of observation, 79% and 66% of patients in the early and late CCRT groups, respectively, had died (Fig. 2b, Table 2). When comparing postoperative CCRT initiation week-by-week, there were significant differences in median OS ($P=0.0005$ using the log-rank test) in the entire cohort (Fig. 2c, Table 2). Pairwise comparisons of the timing of CCRT initiation on a weekly basis revealed no significant differences between any of the pairs that were examined (see Additional file 1).

Univariable analysis demonstrated significant associations (HR [95% CI]; $P<0.0001$ for all) between the following factors and worse OS: old age (1.02 [1.015–1.022]), male sex (1.24 [1.143–1.342]), prolonged postoperative hospitalisation (1.01 [1.005–1.008]), HTN (1.23 [1.134–1.338]), DM (1.30 [1.172–1.451]), and RT initiation as an inpatient (1.31 [1.202–1.437]). Delayed CCRT initiation (> 21 days) and craniotomy followed by tumour resection (vs. biopsy alone) were significantly associated with prolonged OS in the univariable Cox proportional hazards analysis (HR [95% CI], 0.82 [0.741–0.910]; $P=0.0002$ and 0.50 [0.434–0.565]; $P<0.0001$, respectively).

On multivariable analysis, the factors associated (adjusted HR [95% CI]; $P<0.0001$ for all) with worse OS included old age (1.02 [1.015–1.022]), male sex (1.31 [1.208–1.421]), and prolonged postoperative hospitalisation (1.01 [1.005–1.009]), whereas surgical tumour resection (0.50 [0.435–0.577]) was associated with prolonged OS. However, the other variables with a significant association on univariable analysis lacked significance on multivariable analysis (Table 3).

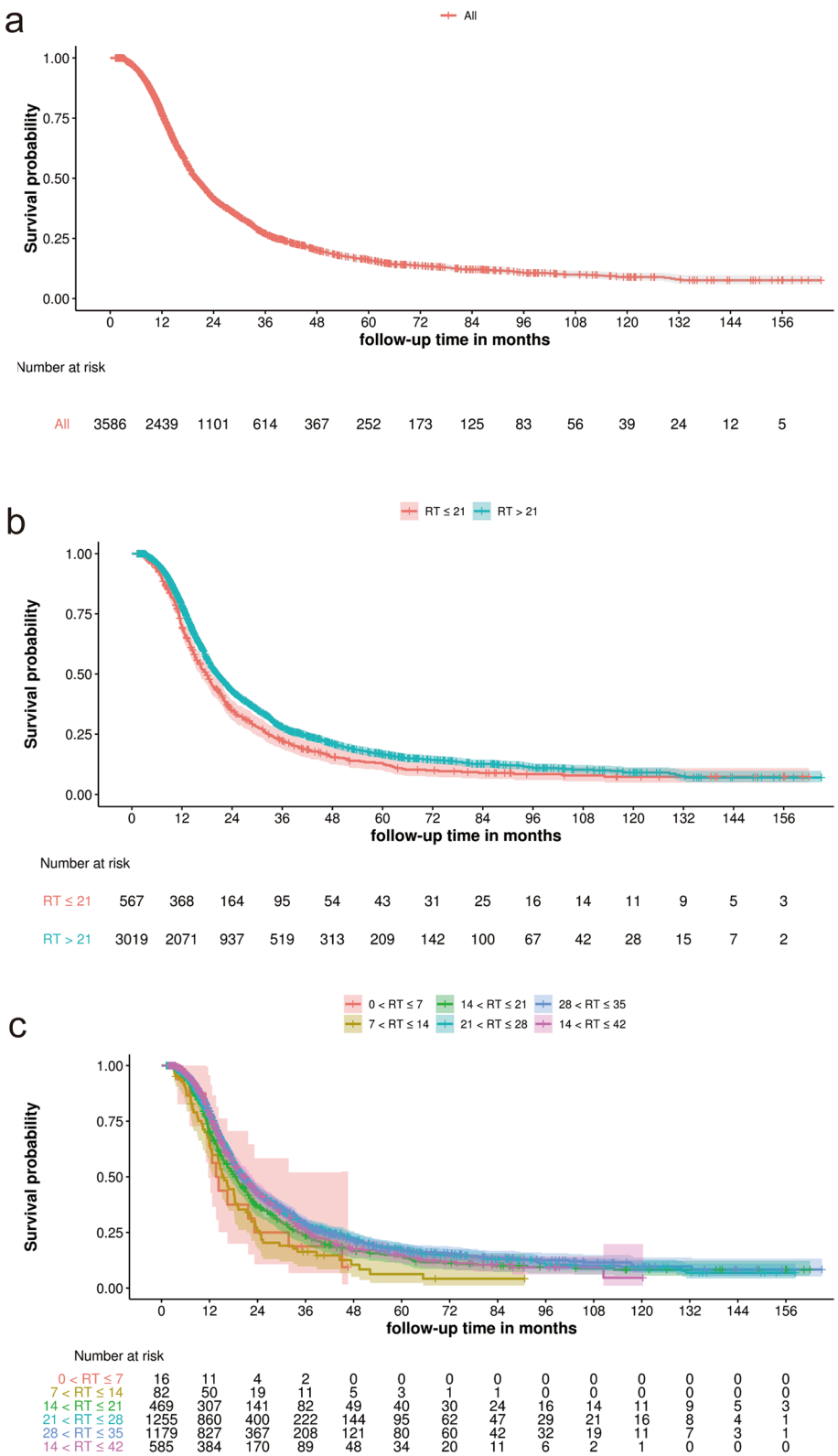

Fig. 2 Overall survival analysis. **a** Kaplan–Meier survival curve of the entire cohort. The median overall survival (OS) period was 19.98 (95% confidence interval [CI], 19.12–20.86) months. **b** Kaplan–Meier survival curves of the early chemoradiotherapy (CCRT) vs. late CCRT groups. The OS periods for the early and late CCRT groups were 17.94 (95% CI, 16.33–19.15) and 20.47 (95% CI, 19.58–21.36) months, respectively ($P=0.0002$). **c** Kaplan–Meier survival curves stratified by each week of CCRT initiation ($P=0.0005$)

Table 2 Kaplan–Meier estimates of the overall survival

	n	Death, n (%)	Median survival months, 95% CI	Log-rank P
Early vs. late CCRT				
Early CCRT (≤ 21 days)	567	447 (78.84)	17.94 [16.33–19.15]	0.0002
Late CCRT (> 21 days)	3,019	2,004 (66.38)	20.47 [19.58–21.36]	
CCRT initiation				
≤ 7 days	16	14 (87.5)	13.95 [11.11–23.23]	0.0005
> 7 and ≤ 14 days	82	71 (86.59)	15.18 [12.49–18.33]	
> 14 and ≤ 21 days	469	362 (77.19)	18.60 [16.59–20.44]	
> 21 and ≤ 28 days	1,255	847 (67.49)	20.70 [19.22–21.95]	
> 28 and ≤ 35 days	1,179	776 (65.82)	20.17 [18.92–21.91]	
> 35 and ≤ 42 days	585	381 (65.13)	20.90 [18.53–22.67]	

CCRT concurrent chemoradiotherapy, *CI* confidence interval

Table 3 Univariable and multivariable analyses for overall survival using a Cox proportional hazards model

Variables	Univariable analysis		Multivariable analysis	
	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Early CCRT (≤ 21 days)	Ref		Ref	
Late CCRT (> 21 days)	0.82 (0.741–0.910)	0.0002	0.98 (0.872–1.091)	0.6663
Age	1.02 (1.015–1.022)	< .0001	**1.02 (1.015–1.022)**	< .0001
Sex, male	1.24 (1.143–1.342)	< .0001	**1.31 (1.208–1.421)**	< .0001
Sex, female	Ref		Ref	
Length of stay	1.01 (1.005–1.008)	< .0001	**1.01 (1.005–1.009)**	< .0001
HTN, yes	1.23 (1.134–1.338)	< .0001	1.02 (0.933–1.120)	0.6340
HTN, no	Ref		Ref	
DM, yes	1.30 (1.172–1.451)	< .0001	1.10 (0.980–1.230)	0.1062
DM, no	Ref		Ref	
Inpatient RT	1.31 (1.202–1.437)	< .0001	1.00 (0.884–1.125)	0.9664
Outpatient RT	Ref		Ref	
Tumour resection	0.50 (0.434–0.565)	< .0001	**0.50 (0.435–0.577)**	< .0001
Biopsy alone	Ref		Ref	

CCRT concurrent chemoradiotherapy, *CI* confidence interval, *DM* diabetes mellitus, *HR* hazard ratio, *HTN* hypertension, *RT* radiotherapy

Subgroup analysis stratified by procedure type (biopsy alone, $n=297$, and surgical tumour resection, $n=3,289$) was performed. In the biopsy group, patients who received early CCRT (≤ 21 days, $n=125$) demonstrated significantly (log-rank $P<0.0001$) longer median OS of compared with those who received late CCRT (> 21 days, $n=172$), with a median OS [95% CI] of 15.93 [14.09–18.40] and 11.83 [10.84–14.16] months, respectively (Fig. 3a). In contrast, patients who received early CCRT (≤ 21 days, $n=442$) after surgical tumour resection had significantly (log-rank $P=0.0009$) shorter median OS than those who received late CCRT (> 21 days, $n=1,859$), with a median OS [95% CI] of 18.50 [16.56–20.63] and 21.32 [20.34–22.51] months, respectively (Fig. 3b). The HR in each subgroup was statistically significant ($P<0.05$), even after adjusting for age, sex, length of hospitalisation, HTN, DM, and admission status (Table 4).

Discussion

In an analysis of national health insurance claims data, our investigation into the optimal timing of postoperative CCRT initiation found that delayed CCRT initiation (> 21 days after surgery) was associated with prolonged overall survival (OS) in univariable analysis. However, this association was not statistically significant in the multivariable analysis, indicating that other factors may have influenced this relationship. Notably, our study is the first to demonstrate a reverse correlation between the CCRT–surgery interval and OS based on the type of surgical procedure; patients who underwent surgical resection benefitted from delayed CCRT, whereas those who underwent biopsy alone experienced shorter survival with delayed CCRT. Previous studies did not distinguish between biopsy and tumour

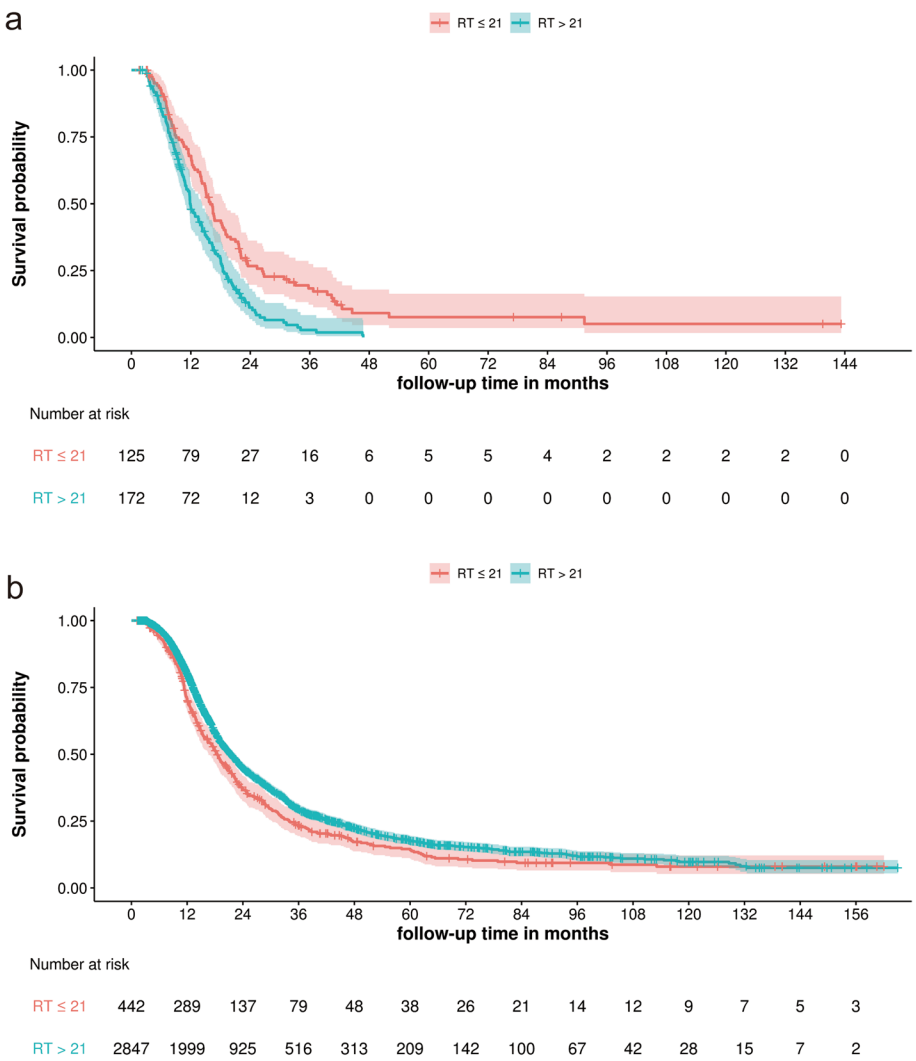

Fig. 3 Survival analysis for subgroups based on surgical intervention. **a** Kaplan–Meier survival curve of the biopsy group stratified by radiotherapy (RT) timing. The overall survival periods were 15.93 (95% confidence interval [CI], 14.09–18.40) and 11.83 (95% CI, 10.84–14.16, $P=0.0001$) months in the early and late chemoradiotherapy (CCRT) groups, respectively. **b** Kaplan–Meier survival curve of the surgery group stratified by RT timing. The overall survival periods were 18.50 (95% CI, 16.56–20.63) and 21.32 (95% CI, 20.34–22.51, $P=0.0009$) months in the early and late CCRT groups, respectively

Table 4 Subgroup analysis according to procedure

	n	Death, n (%)	Median survival months, 95% CI	*P*	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)[a]	*P*
Biopsy								
Early CCRT (≤ 21 days)	125	102 (81.60)	15.93 [14.09–18.40]		Ref		Ref	
Late CCRT (> 21 days)	172	145 (84.30)	11.83 [10.84–14.16]	< .0001	1.72 [1.322–2.235]	< .0001	1.80 [1.378–2.346]	< .0001
Tumour resection								
Early CCRT (≤ 21 days)	442	345 (78.05)	18.50 [16.56–20.63]		Ref		Ref	
Late CCRT (> 21 days)	2,847	1,859 (65.30)	21.32 [20.34–22.51]	0.0009	0.82 [0.734–0.923]	0.0009	0.85 [0.752–0.955]	0.0065

RT radiotherapy

[a] Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using multivariable Cox proportional hazards models, adjusting for age, sex, length of stay, hypertension, diabetes mellitus, and type of hospital service

resection. The differing proportions of biopsy and resection patients across studies may explain the variability in results, as well as different institutional policies favouring subtotal or total resection, which could have impacted survival outcomes.

Despite extensive discussions on the impact of the surgery–CCRT interval on the OS of patients with GBM, a consensus on the timing of CCRT remains elusive, thereby complicating treatment planning. Earlier studies have indicated that delayed CCRT can prolong OS [9–16]; however, these studies often excluded treatment initiation periods beyond six weeks postoperatively, which might have led to skewed population for investigation. Conversely, studies advocating earlier CCRT are based on smaller patient cohorts, leading to questionable results [4, 17, 18].

In this study, we screened 8,738 patients using the ICD-10 code C71 [28], which includes both GBM and low-grade gliomas, such as oligodendrogliomas, within a specified period and found that CCRT and TMZ was exclusively used in GBM treatment. When compared with the 5,796 patients with GBM who were identified through a national cancer registry between 2007 and 2016 [29], our patient count is deemed accurate, after accounting for different study durations. Most of the study cohort completed the standard six cycles of TMZ, indicating that the included patients received appropriate GBM treatment. The OS of the total study population was comparable with the previously reported median OS of 15 months [1, 2].

The categorisation into early and late CCRT groups was based on a 21-day median interval between surgery and CCRT initiation. The analysis revealed a significantly longer OS in the late CCRT group, despite a larger proportion receiving delayed treatment. Early initiation of CCRT may increase the risk of hypoxic conditions in the postoperative tumour bed, which can reduce the effectiveness of radiotherapy, as oxygen is crucial for radiation-induced DNA damage. Additionally, early CCRT may impair the patient's immune response, particularly cell-mediated immunity, which is essential for tumour control. Delayed CCRT allows for tissue recovery, improved vascularisation, and a more robust immune response, potentially contributing to prolonged OS [4, 14, 30]. Kaplan–Meier estimates varied significantly by the CCRT initiation week; however, pairwise comparisons did not show significant differences after day 21, suggesting no substantial OS variance by CCRT initiation week. Nonetheless, further research is warranted to determine the most advantageous timing for postoperative CCRT.

Clinically, our findings suggest that for patients who have undergone tumour resection, there is no need to rush the initiation of CCRT within 21 days solely to improve survival. Since molecular biomarkers are critical for obtaining an accurate diagnosis and typically take over three weeks to become available after surgery, waiting for these results before starting CCRT is unlikely to negatively impact prognosis. The key point here is not to recommend delaying CCRT beyond the fourth week but rather to indicate that starting within the first three weeks may not be essential for improved outcomes. This approach aligns with other research indicating that delayed CCRT initiation within six weeks does not compromise survival in patients with GBM [13, 14]. In contrast, for patients who have only had a biopsy, earlier initiation of CCRT may be more advantageous. Decisions on CCRT timing should also consider tumour characteristics, extent of resection, and the patient's overall health.

Risk factor analysis for OS identified that age, sex, and surgery type (resection vs. biopsy) were correlated with survival. Due to the retrospective nature of the claims data, detailed patient characteristics could not be precisely determined; therefore, the duration of hospitalisation was used as a proxy for patient performance. Patients receiving early CCRT were more likely to have extended hospital stays, suggesting lower performance status. In contrast, those with comorbidities tended to receive late CCRT, with early treatment typically starting upon hospitalisation. Notably, the duration of hospitalisation emerged as a significant independent variable, which is potentially indicative of performance status.

The hypothesis that optimal CCRT timing may differ due to residual tumour size post-biopsy or resection was considered. Our findings were contradictory and statistically significant for both patient groups, underscoring the need for early CCRT in patients who are unable to undergo complete tumour resection [22]. Further subgroup analysis on the extent of resection within the tumour resection group may unveil additional differences, such as the benefit of earlier CCRT initiation following partial resection. This should be the subject of future studies. Unlike immutable prognostic factors, such as MGMT gene promoter methylation [8], CCRT timing is a modifiable treatment aspect with significant OS implications. Therefore, our study's goal was to ascertain the optimal CCRT initiation timing through retrospective analysis of a substantial patient cohort.

Limitations

The retrospective design and incomplete data of this study pose several limitations. The absence of molecular data, including gene transcription, genetic alterations, and DNA methylation profiles, restricts their use as prognostic indicators. Furthermore, the lack of IDH mutation data, a crucial survival factor for gliomas, significantly hinders the comprehensive analysis of patient outcomes.

To address potential confounding factors, a multivariable analysis was performed for patients presenting with seizures, indicative of gliomas with IDH mutations [31].

The difference in sample sizes between the early ($n=442$) and late ($n=2,847$) CCRT groups may have statistical implications, as the smaller early CCRT group may limit statistical power and increase the risk of type I errors. Moreover, as the log-rank test has limitations, particularly in small sample sizes, novel nonparametric tests could be considered for future research [32].

In addition, we could not include important prognostic factors such as tumour location and size in the multivariable analysis due to the limitations of the National Health Insurance claims database. Future studies with more comprehensive datasets should consider these factors to provide a more accurate assessment of the impact of CCRT timing on survival outcomes.

Another critical limitation arises from the nature of health insurance claims data, which inherently lacks the granularity to accurately ascertain the cause of death. Consequently, this study relied on all-cause mortality as the endpoint, introducing a significant constraint in distinguishing between tumour-specific outcomes and deaths due to other causes.

Additionally, the use of the duration of hospitalisation as a surrogate for patient performance status, despite showing statistical significance, underscores the challenge in directly assessing critical clinical variables [33]. The dataset's limitations in determining the extent of resection further complicate the ability to make precise recommendations regarding CCRT timing. Future research, with a focus on categorising types of surgeries, is essential to overcome these obstacles and refine treatment strategies.

Conclusion

Our large-scale, population-based study, which included over 3,000 cases, suggests that the timing of CCRT initiation may have differential impacts on overall survival (OS) in patients with newly diagnosed GBM depending on the surgical approach. Specifically, initiating CCRT more than three weeks after tumour resection is associated with prolonged OS, while earlier initiation (≤ 21 days) is linked to better outcomes in patients who undergo biopsy alone. These findings highlight that the optimal timing for CCRT may need to be individualized based on resection status, a critical consideration that could enhance clinical decision-making in GBM management.

Abbreviations

CCRT	Concurrent chemoradiotherapy
CI	Confidence interval
DM	Diabetes mellitus
GBM	Glioblastoma
HIRA	Health Insurance Review and Assessment
HR	Hazard ratio
HTN	Hypertension
ICD-10	International Classification of Diseases, 10th revision
OS	Overall survival
RT	Radiotherapy
TMZ	Temozolomide

Supplementary Information

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Additional file 1. Adjustment for multiple comparisons for the log rank test.

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Authors' contributions

DL contributed to the conceptualisation, methodology, formal analysis, investigation, and writing the original draft. EL contributed to the conceptualisation, methodology, formal analysis, investigation, and writing the original draft. THR contributed to the conceptualisation, methodology, formal analysis, investigation, and reviewing and editing the manuscript. S-HK contributed to the conceptualisation, methodology, and reviewing and editing the manuscript. All authors read and approved the final manuscript.

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Data availability

The patient data included in this study were collected from the Korean Health Insurance Review and Assessment Service (HIRA) database (https://opendata.hira.or.kr/).

Declarations

Ethics approval and consent to participate

The study protocol adhered to the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 1983, and was approved by the Institutional Review Board of Ajou University Hospital (approval number: AJOUIRB-EX-2022-314). As this study utilized previously collected data from the National Health Insurance claims database, the requirement for informed consent was waived.

Consent for publications

Not applicable.

Competing interests

The authors declare no competing interests.

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