



Comparative analysis of hypofractionated short-course versus standard radiation therapy in elderly patients with glioblastoma: analysis of nationwide database

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Abstract

Purpose Hypofractionated short-course radiation therapy (SCRT) is an alternative treatment option for elderly or frail patients with newly diagnosed glioblastoma (GBM) post-surgery. This study compares survival outcomes and treatment costs between patients receiving SCRT and those undergoing standard long-course radiation therapy (LCRT).

Methods This retrospective study utilized health insurance claims and national cancer registry data from Korea to compare overall survival (OS) and treatment costs between patients receiving SCRT and LCRT across all ages and sub-group analysis within the subgroup of cases aged 65 and older from 2016 onwards, a period when intensity-modulated radiotherapy (IMRT) was widely adopted.

Results A total of 1,598 patients were included. Median OS since the first day of radiation therapy was 10.4 months (95% CI [9.6; 12.8]) for SCRT ($n=197$) versus 16.2 months (95% CI [15.5; 16.9]) for LCRT ($n=1401$) respectively. Subgroup analysis using stabilized inverse probability of treatment weighting (S-IPTW) showed indicating non-inferiority in elderly patients in median OS for elderly patients (≥ 65) with 10.6 months (95% CI [8.9; 14.0]) for SCRT ($n=147$) versus 13.2 months (95% CI [8.9; 14.0]) for LCRT ($n=541$). The median treatment cost of SCRT is about 6,000 USD lower, 25% less than LCRT. Compliance with the standard TMZ regimen post-radiation improved OS across all age groups.

Conclusion Considering comparable OS and shorter treatment duration, SCRT offers a viable, cost-effective option for elderly GBM patients. Adhering to standard TMZ also contributes to OS improvement. Further research reflecting key prognostic factors is essential to refining the role of SCRT.

Keywords Glioblastoma · Adjuvant radiotherapy · Elderly patients · Temozolomide · Overall survival · Cost-effectiveness

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Introduction

Glioblastoma (GBM) is a highly aggressive malignancy with a poor prognosis accounting for 14.2% of all newly diagnosed brain tumors and 50.9% of all malignant brain tumors [1, 2]. Incidence varies by race, with non-Hispanic whites having a rate of 22.31 per 100,000, while Asian populations, including Korea, report lower rates of 7.47 per 100,000 for malignant gliomas, including GBM [3]. The median overall survival (OS) for GBM remains poor at 10 to 14 months [1, 2, 4, 5]. The current standard of care includes surgical resection followed by chemoradiation with temozolomide (TMZ) and adjuvant TMZ therapy after radiation therapy (RT) [6–8].

Standard RT for GBM typically administers 60 Gy (Gy) of radiation after surgical resection over 30 sessions [6, 7, 9]. However, this can be challenging for elderly and frail patients. To address this, hypofractionated short-course radiation therapy (SCRT) has been developed. Clinical trials conducted by the Nordic Clinical Brain Tumour Study Group [10] (34 Gy in 10 fractions) and Roa et al. [11, 12] (40 Gy in 15 fractions and 25 Gy in 5 fractions) have validated the efficacy and safety of SCRT, making it a viable alternative for elderly and frail patients, as endorsed by major treatment guidelines [6–8].

Despite clinical trials, there is not much information available about the outcomes of SCRT in real-world practice. Some studies with real-world data [13, 14] reported that SCRT has an inferior OS than standard long-course radiation therapy (LCRT). However, these studies were done when 2D or 3D RT was the main technique. Today, advanced RT methods like intensity-modulated RT (IMRT), which reduce RT-induced toxicity [15, 16], are more common. Therefore, further research is needed to determine if these advancements impact OS in real-world practice.

We have confirmed that the health insurance claims database of Korea can effectively be used to analyze treatment outcomes for SCRT, integrating with the national cancer registry and survival data through government-managed registration [17, 18]. This study aims to evaluate the OS and RT costs of the patients with GBM treated with SCRT compared to those treated with LCRT in the IMRT era. Also, we have conducted a specific analysis focused on the elderly patient group aged 65 and over to assess their eligibility for SCRT based on treatment guidelines.

Materials and methods

Data sources and access process

Data analysis was performed based on national health insurance claims data and patient registry data of Korea. To ensure public interest and anonymity, data integration from related institutions was conducted through an application review by Korea Healthcare Bigdata Service (<https://hcdl.mohw.go.kr/>) of Korea Health Information Service (KHIS). The researchers obtained IRB review and approval from the affiliated institution. Data analysis was conducted only in the closed network at KHIS, and only approved results were allowed to be exported.

Study population

The initial case selection was based on the Korean National Cancer Registry managed by the Korea National Cancer

Center (KNCC). This database uses the International Classification of Diseases for Oncology (ICD-O) [19], to identify GBM patients (coded 944_._) among those with C71 in the International Statistical Classification of Diseases (ICD). We selected cases registered between January 1, 2016, and December 31, 2021, following the introduction of IMRT reimbursement in 2015. Anonymized linkage keys were used to join data with other databases.

The second database was the Health Insurance Review and Assessment Service (HIRA) database, which has information on treatment records, costs, RT sessions, and schedules. Patients who were treated for less than 12 RT sessions were excluded to rule out incomplete treatment or RT with a palliative aim. Additionally, patients with > 30 days interval between RT sessions or those starting RT 90 or more days after surgery were excluded, as this suggested treatment interruption or re-irradiation. Proton RT cases were excluded for consistency. Survival data were obtained from the National Health Insurance Service database (Fig. 1).

Statistical methods

Demographics were reported as medians, standard deviations (SD), and 95% confidence intervals for continuous variables, with normality assessed by the Shapiro-Wilk test. Continuous variables, which did not follow a normal distribution, were compared using the Mann-Whitney U test. Categorical variables were presented as counts and proportions and analyzed using the chi-square test. An imbalance in age and chemotherapy status between SCRT and LCRT groups was identified using the standardized mean difference, and confounders were adjusted using the Propensity Score method with Stabilized Inverse Probability of Treatment Weighting (S-IPTW) [20].

The primary endpoint was OS from the first day of RT to evaluate outcomes of treatment focusing on RT with Kaplan-Meier methods. Due to GBM's short survival duration, the Gehan-Breslow and log-rank tests were used to assess statistical differences, and non-inferiority and HR consistency were tested with the Cox proportional hazards regression model, adjusting for imbalances via S-IPTW.

The secondary endpoint, total treatment cost, was analyzed using the Mann-Whitney U-test due to non-normal distribution, with a 2-sample t-test for mean values. Exploratory endpoints examined the impact of concurrent and adjuvant TMZ on treatment outcomes and costs.

All statistical analyses were performed using R Studio (version 4.2.2_2022, RStudio, PBC, Boston, MA, USA), with packages of 'survival', 'survminer', 'survey', and 'ggplot2'.

Fig. 1 Diagram of case selection and data joining process

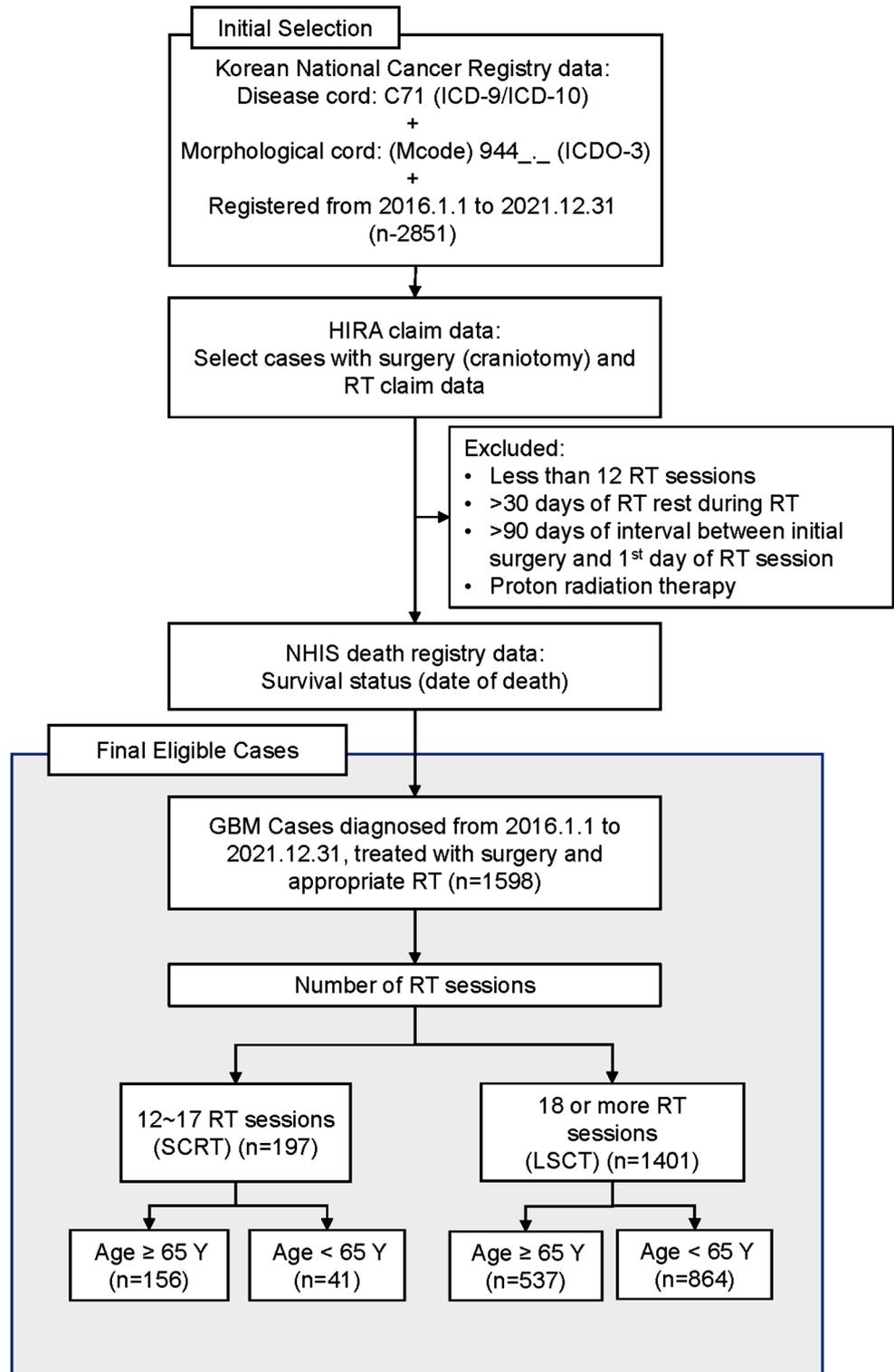
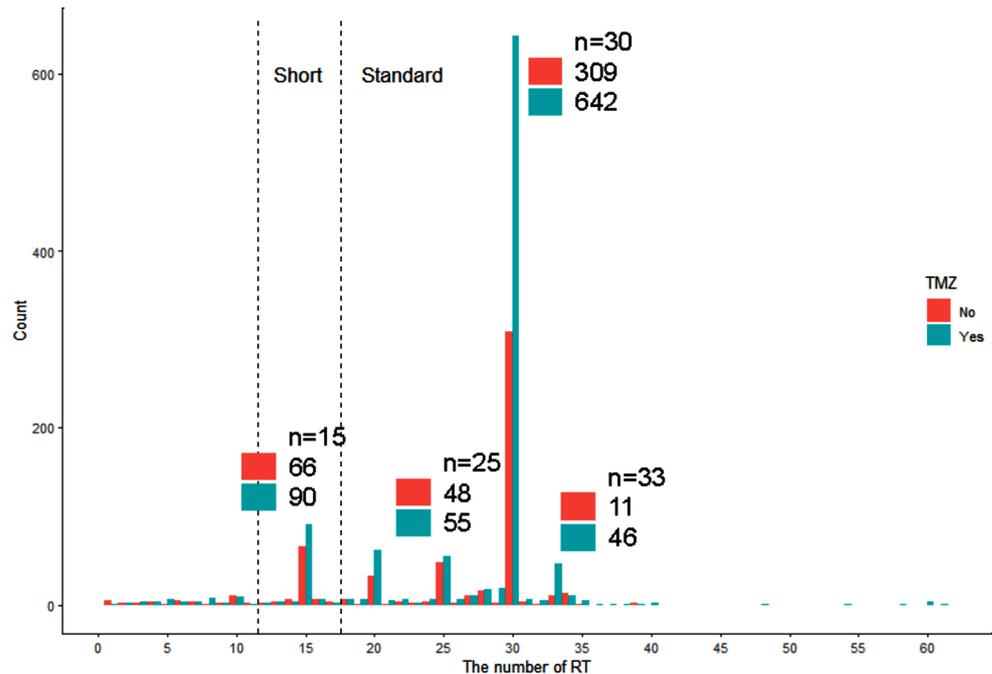


Table 1 Characteristics among SCRT and LCRT group

Baseline Characteristics	Original population (<i>n</i> = 1598)			Weighted population after IPTW (<i>n</i> = 1641)		
	SCRT (<i>n</i> = 197)	LCRT (<i>n</i> = 1401)	SMD	SCRT (<i>n</i> = 242)	LCRT (<i>n</i> = 1399)	SMD
Age, Years						
Median	70	60	0.987	55	60	0.371
Mean ± SD	68.76 ± 9.97	57.03 ± 13.53		52.82 ± 16.60	58.44 ± 13.58	
Elderly, <i>n</i> (%)			0.772			0.127
≥ 65 years	156 (79.2)	537 (38.3)		147 (60.7)	541 (38.7)	
Gender, <i>n</i> (%)			0.133			0.293
Male	108 (54.8)	860 (61.4)		112 (46.2)	848 (60.6)	
Female	89 (45.2)	541 (38.6)		130 (53.8)	551 (39.4)	
Temozolomide, <i>n</i> (%)			0.240			0.250
Treated	108 (54.8)	932 (66.5)		128 (52.9)	911 (65.1)	
Untreated	79 (45.2)	469 (33.5)		114 (47.1)	488 (34.9)	
RT fraction, <i>n</i>						
Median	15	30	4.803	15	30	4.723
Mean ± SD	14.92 ± 0.75	28.94 ± 4.06		14.85 ± 0.87	28.86 ± 4.10	

SCRT: Hypofractionated short-course radiation therapy, LCRT: Standard long-course radiation therapy, SD: Standard deviation, SMD: Standardized mean difference

Fig. 2 Histogram of total fraction number of radiation therapy by age group (Elderly vs. non-Elderly)



Results

Accrual

A total of 2,851 cases were identified in the KNCC database, with 1,598 GBM cases deemed eligible (Fig. 1). Among them, 197 cases were treated with SCRT. The SCRT group had a median age of 70 years (mean ± SD: 68.76 ± 9.97), compared to 60 years (mean ± SD: 57.03 ± 13.53) in the LCRT. Of the total, 693 cases were aged ≥ 65, with 79.2% (156/197) of the SCRT group in this age range (Tables S1,

S2). Men represented 60.6% of the cases, and 65% were prescribed TMZ during treatment (Table 1).

Characteristics of RT

The majority of SCRT cases received 15 RT sessions (*n* = 156). In the LCRT group, 30 sessions were most common (*n* = 951), followed by 25 (*n* = 103) and 33 (*n* = 57). Alternative SCRT schedules of 5 or 10 sessions were rare (Fig. 2) and excluded from analysis. The interval between surgery and RT initiation was also examined (Table S3,

Figure S2). Although the median interval showed no significant difference, the third quartile was higher in the SCRT group, particularly among those under 65.

Overall survival

The median OS for all 1,598 subjects, starting from the first date of RT, was 15.6 months (95%CI: 14.9–16.4). When categorized by age group, the median OS for the elderly group was 12.7 months (95%CI: 11.7–13.7) and the median OS of the non-elderly group was 18.2 months (95%CI: 16.9–19.7). Regarding the RT course, SCRT cases ($n=197$) had a median OS of 10.4 months (95%CI: 9.6–12.8), while LCRT ($n=1401$) had a median OS of 16.2 months (95%CI: 15.5–16.9). To account for potential confounding factors that could affect OS, a statistical analysis comparing SCRT and LCRT was conducted using pseudo-data generated by S-IPTW (Tables S1, S2). With this data, the median OS of all cases was 12.8 months (95%CI: 10.7–13.7) for the SCRT ($n=242$) compared to 15.9 months (95%CI: 15.1–16.6) for the LCRT ($n=1399$), yielding a hazard ratio (HR) of 1.296 (95%CI: 0.937–1.726). The non-inferiority HR margin was set at 1.32 and the p -value was 0.4498, the inferiority could not be rejected, revealing a statistically significant difference in OS among all cases (Fig. 3A). However, in the elderly group aged 65 or more, the median OS was 10.6 months (95%CI: 8.9–14.0) for the SCRT ($n=147$) compared to 13.2 months (95%CI: 12.1–14.0) for the LCRT ($n=541$), yielding an HR of 1.043 (95%CI: 0.8545–1.273). The p -value for the non-inferiority test was 0.0152, indicating rejection of inferiority and confirming no statistical difference between SCRT and LCRT (Fig. 3B). In the non-elderly group, the difference in median OS between SCRT ($n=40$) and LCRT ($n=864$) was more pronounced with 10.9 months (95%CI: 9.9–18.4) for SCRT versus 18.7 months (95%CI: 17.3–20.2) for LCRT. The HR was 1.846 (95%CI: 1.117–2.894) and the p -value for the non-inferiority test was 0.9280 (Fig. 3C).

Treatment cost

A statistically significant difference in median total treatment costs was shown that the SCRT group's cost was 6,480 USD less, corresponding to 25% of the 25,847 USD than the LCRT. This difference was more pronounced in cases with TMZ, where the median treatment cost for the SCRT was 11,180 USD less than the LCRT, corresponding to 31% of the 35,576 USD (Table 2).

Effect of temozolomide

Survival analysis was conducted by age group to assess the impact of concurrent TMZ. In the elderly group, no

significant difference in OS was observed between those with and without concurrent TMZ (13.4 (95%CI: 11.8–14.3) vs. 12.2 months, (95%CI: 10.2–13.9)). In the group under 65, although the OS difference between those with and without TMZ was statistically different (18.1 months (95%CI: 16.7–19.7) vs. 18.4 months (95%CI: 16.0–21.2), $p=0.026$), however, it was only 7 days (Figure S3). Among the concurrent TMZ cases ($n=1,039$), 366 cases without TMZ treatment after RT had a median OS of 13.4 months (95%CI: 11.7–15.9), while 673 cases with TMZ prescription at least once after RT had a median OS of 16.5 months (95%CI: 15.3–17.3) (Figure S4).

Among the 673 cases with TMZ after RT, an in-depth analysis was conducted on the standard TMZ treatment entailing at least five five-day TMZ cycles after RT (Figure S5). After S-IPTW, the median OS for those completing the standard schedule was 22.5 months (95%CI: 20.2–24.6), compared to 12.3 months (95%CI: 11.4–13.6) for cases that did not. The HR was 0.521 (95%CI: 0.439–0.617, p -value < 0.001) (Figure S6A). Both elderly (22.1 vs. 11.5 months, Figure S6B) and non-elderly (23.6 vs. 13.2 months, Figure S6C) groups showed a similar survival benefit in the standard TMZ schedule.

Discussion

In this study, the median OS of all cases was 15.6 months, slightly longer than the previously reported OS of 10–14 months for GBM patients [1, 4, 5]. However, this OS result is marginally poorer than the OS results of 16–20 months from the clinical trials with standard treatment for newly diagnosed GBM [21, 22]. The primary endpoint of this study was to the effect of SCRT on survival. In all ages, SCRT showed significantly inferior results in OS than LCRT. However, when limited to cases aged 65 and over, the statistical analysis showed that the OS of SCRT was not inferior to LCRT's. This result was consistent with randomized trial results [10, 11]. The choice of defining elderly at 65 years old might be subject to some disagreement, as some consider 70 as the cut-off [14], while 60 was also selected as the cut-off in some studies [23]. We used a cut-off of 65 for the elderly based on benchmark studies [11, 24, 25].

In this study, SCRT primarily followed a schedule of 40 Gy in 15 fractions, while LCRT mostly used a schedule of 60 Gy in 30 fractions ($n=951$) followed by 33 fractions and 58.5 Gy in 25 fractions [26] (Fig. 2). Comparing 40 Gy in 15 fractions and 60 Gy in 30 fractions from a radiobiology perspective, SCRT has a lower Biological Effective Dose (BED) of RT in tumor cells. The BED for GBM, not regarding tumor doubling time during treatment, is calculated as follows: total dose \times [1 + daily dose/(α/β ratio)] [27].

Fig. 3 Overall survival. All age (a), Elderly (b), and non-Elderly (c) group after S-IPTW applied curved by RT courses among all cases. The number of cases at risk over time is shown below the curves

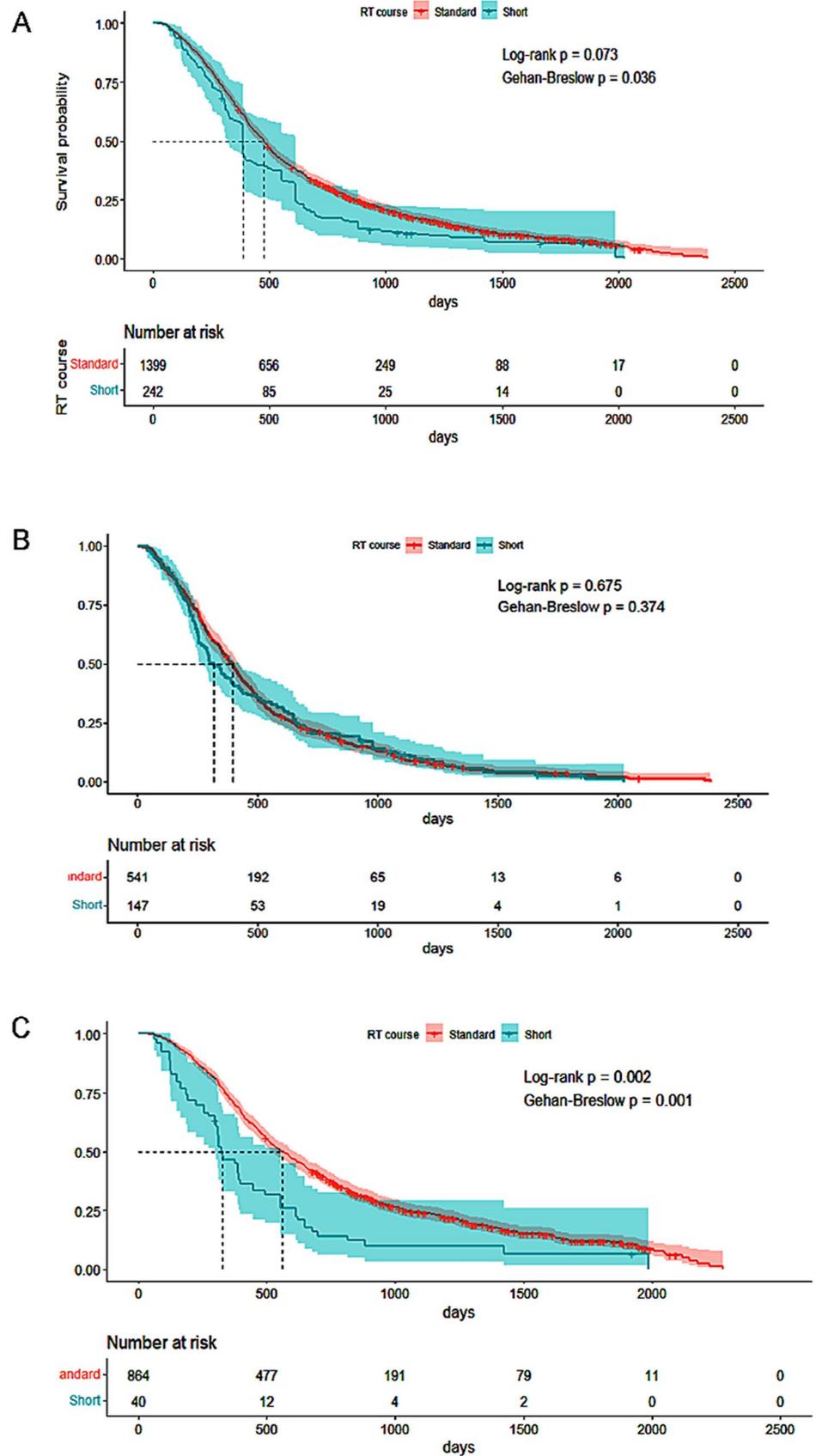


Table 2 Total treatment cost based on claimed to HIRA during RT

	SCRT	LCRT	<i>p</i> -value*
All cases			
Cost, KRW(USD)†			
Median	26,144,800 (19,367)	34,893,280 (25,847)	< 0.001
IQR	17,905,660– 56,075,260	31,626,680– 62,036,020	
Case treated with Temozolomide			
Cost, KRW(USD)†			
Median	32,934,290 (24,396)	48,028,220 (35,576)	< 0.001
IQR	20,532,245– 60,460,840	32,672,880– 77,424,270	
Case treated without Temozolomide			
Cost, KRW(USD)†			
Median	19,447,860 (14,405)	32,457,970 (24,043)	< 0.001
IQR	16,775,760– 39,897,500	28,525,925– 34,582,305	
≥ 65 years			
Cost, KRW(USD)†			
Median	26,970,800 (19,978)	35,465,320 (26,271)	< 0.001
IQR	17,905,660– 56,602,440	31,396,460– 60,559,560	
< 65 years			
Cost, KRW(USD)†			
Median	25,170,660 (18,645)	34,755,790 (25,745)	< 0.001
IQR	18,211,220– 46,353,040	31,743,975– 64,046,055	

*: from Mann-Whitney U-test, †: 1 US dollar (USD)=1350 Korean Won (KRW)

Generally, GBM cells are estimated to have an α/β ratio of 8 Gy (range, 5.0–10.8 Gy) [28], which is higher than normal central nerve system tissues' α/β ratio of 2 Gy. By this, a BED of GBM was calculated as 53.42 Gy₈ in SCRT and 75 Gy₈ in LCRT. Theoretically, LCRT may represent superior GBM cell killing and tumor control. This point could be evidence of the superior OS result of the LCRT in all age groups. Despite this, the BED in normal brain tissue was also higher in LCRT with 120 Gy₂ than SCRT's 93.25 Gy₂ and this would increase the risk of RT-induced toxicity, especially in elderly and fragile patients with poor general performance [29].

The OS result of this study contrasted with some studies with real-world data in elderly patients. Haque et al. [13], investigated 5126 patients aged 65 years or more and found a statistically significant difference in OS (6.2 for SCRT vs. 10.7 months for LCRT). Mak et al. [14] have conducted a similar study on the elderly aged 70 years or more and found a difference in OS (4.9 for SCRT vs. 8.9 months for LCRT). Otherwise, the meta-analysis by Trone et al. [30].

demonstrated that SCRT can achieve comparable survival outcomes. We prudently hypothesize that this difference in OS between SCRT and LCRT compared to past studies might be attributed to approximately two reasons.

First, the difference in RT technique may be a contributing factor. The previous trials did not provide detailed information on the RT techniques used, but most cases in this study were treated with IMRT, including volumetric-modulated arc therapy (VMAT). Although the total BED for normal brain tissue in SCRT is lower than in LCRT, the higher daily dose in SCRT may increase the risk of acute toxicity, potentially leading to treatment interruptions. IMRT can theoretically improve the conformality of RT and reduce unnecessary radiation exposure to normal brain tissue compared to 3D RT [31]. Thibouw et al. [15], highlighted IMRT's benefit in reducing neurological side effects, although some studies found it did not significantly improve OS [15, 32]. VMAT allows for movement of the linear accelerator during radiation delivery, providing a more conformal dose distribution than early IMRT [33, 34]. Navarra et al. [16] reported that VMAT could improve OS in high-grade glioma compared to 3-D RT. The widespread use of VMAT during the accrual period may contribute to the outcomes observed in elderly groups. However, further research is needed to confirm this hypothesis.

Second, significant differences in proportions of SCRT and LCRT patients may have influenced the results. In both Haque et al. (126/5,000) and Mak et al. (304/4,294), LCRT outnumbered SCRT and it may affect statistical analysis and reflect that SCRT was electively administered to more fragile patients. Both studies included the Charlson–Deyo comorbidity index [35] showing a statistical difference between SCRT and LCRT.

Another potential debate is the selection of 18 as the cut-off between SCRT and LCRT. Given the variability in real-world treatment, which may not strictly follow scheduled RT fractions, we set the criteria based on a range. Although some studies investigated 20 sessions as SCRT [13, 36], we set the dividing point between 15 and 20 fractions to align with current major guidelines, which typically recommend 40 Gy in 15 fractions [6, 9]. However, there is no evidence that any SCRT schedule is superior [37].

To our knowledge, a cost comparison of SCRT and LCRT in GBM has not been previously reported. This study found that SCRT reduced approximately 25% or about 6,000 USD. With the rising costs of advanced treatments, financial toxicity is a growing concern [38]. Studies on cost savings with SCRT have been conducted in breast and prostate cancer [39, 40], reporting 24–39% of the cost savings of SCRT in breast cancer [41, 42]. Reducing RT duration by three weeks within a 15-month life expectancy may offer invaluable time for GBM patients. In countries with limited

RT facilities, shorter treatments could also free up capacity, potentially treating 14 more patients per month, as reported in an Australian study [42].

Regarding the effect of standard TMZ, the role of adjuvant TMZ following RT has been established [43, 44], also in the SCRT setting [24]. In this study, while the initial analysis did not find a difference in OS based solely on the presence or absence of TMZ, completing the full TMZ schedule may improve survival outcomes across all age groups (Figure S6).

The following limitations should be considered when interpreting the results. First, this study does not include crucial prognostic factors such as O⁶-methylguanine-DNA methyltransferase (MGMT) methylation, patient's performance, and tumor characteristics including the extent of surgical resection. In GBM, the status of the MGMT is known as a key factor influencing the treatment outcomes of TMZ [25, 45] and the isocitrate dehydrogenase (IDH) mutation as well [46]. In Korea, the recently reported percentage of MGMT methylation in GBM is 42.4% and 6.2% for IDH-1 mutation [46]. The lack of MGMT information was also noted in previous studies [13, 14, 47].

The absence of the patient's performance status is another limitation. The database was unable to assess the medical records of cases, which is essential for evaluating performance status like the Karnofsky Performance Status. Indeed, the Charlson-Comorbidity Index suggested as an alternative indicator of patients' performance, was not extracted from the current database. Instead, we investigated the interval between surgery and RT, which may indirectly infer the patient's recovery status after surgery, caution is still required in interpreting the results. (Table S3, Figure S2).

The absence of tumor characteristics, such as the tumor's size, location, and extent of surgery, was another limitation of this study. Although similar limitations were observed in similar studies, the degree of surgical resection was investigated in those studies [13, 14, 47]. Additionally, it's important to note that the study population is highly homogeneous, consisting mostly of Asian ethnicities [48].

Even considering the above limitations, this study provides updated information on SCRT in GBM treatment compared to LCRT reflecting evolved RT techniques. To address the limitations above, KHIS has developed a data-joining process to access the individual medical records of treatment institutions. If this development process is completed, further research should be carried out for more accurate information on SCRT.

Conclusion

This study demonstrates that SCRT offers a viable treatment option for elderly GBM patients, with statistically non-inferior OS to LCRT in patients aged 65 or older. SCRT presents advantages, including reduced treatment costs by 25% with shorter treatment duration. The study also demonstrates completing standard TMZ following RT contributed to the improved OS. However, the limitations of the study, the absence of MGMT status, performance status, and tumor characteristics should be considered when interpreting the results and further research is needed to reflect those.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s11060-024-04853-6>.

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Author contributions Conception and design: Y.K.W, E.S.K, I.Y.J, H.J.O, S.M.L, I.D.Y, S.P.H, J.W.L, J.H.S, H.S.J Collection and assembly of data: Y.K.W, I.N.Y, N.Y.K Data analysis and interpretation: Y.K.W, H.J.O, J.H.S, N.Y.K, H.S.J Manuscript writing: All authors Final approval of manuscript: All authors.

Data availability The anonymized joint database used in this study was analyzed within Korea Healthcare Bigdata's computing facilities where external data removal was prohibited. Researchers only possessed results allowed for external release. Data access and reanalysis are possible within 2024. Any inquiries regarding this study's data and statistics should be directed to the first author at yong.won@schmc.ac.kr.

Declarations

Competing interests The authors declare no competing interests.

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