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Original Article

Choosing Wisely between Radiotherapy Dose-Fractionation Schedules: The Molecular Graded Prognostic Assessment for Elderly Glioblastoma Patients

Hye In Lee[1,2], **Jina Kim**[3], **In Ah Kim**[4], **Joo Ho Lee**[1], **Jaeho Cho**[3], **Rifaquat Rahman**[5], **Geoffrey Fell**[6], **Chan Woo Wee**[3,7], **Hong In Yoon**[3]

[1]Department of Radiation Oncology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, [2]Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, [3]Department of Radiation Oncology, Yonsei Cancer Center, Heavy Ion Therapy Research Institute, Yonsei University College of Medicine, Seoul, [4]Department of Radiation Oncology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea, [5]Department of Radiation Oncology, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA, [6]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA, USA, [7]Department of Radiation Oncology, SMG-SNU Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea

Purpose This study aimed to develop a graded prognostic assessment (GPA) model integrating genomic characteristics for elderly patients with glioblastoma (eGBM), and to compare the efficacy of different radiotherapy schedules.

Materials and Methods This multi-institutional retrospective study included patients aged ≥ 65 years who underwent surgical resection followed by radiotherapy with or without temozolomide (TMZ) for newly diagnosed eGBM. Based on the significant factors identified in the multivariate analysis for overall survival (OS), the molecular GPA for eGBM (eGBM-molGPA) was established.

Results A total of 334 and 239 patients who underwent conventionally fractionated radiotherapy (CFRT) and hypofractionated radiotherapy (HFRT) were included, respectively, with 86% of patients receiving TMZ-based chemoradiation. With a median follow-up of 17.4 months (range, 3.3 to 149.9 months), the median OS was 18.7 months for CFRT+TMZ group, 15.1 months for HFRT+TMZ group, and 10.4 months for radiotherapy alone group (CFRT+TMZ vs. HFRT+TMZ: hazard ratio [HR], 1.52; p < 0.001 and CFRT+TMZ vs. radiotherapy alone: HR, 2.52; p < 0.001). In a combined analysis with the NOA-08 and Nordic trials, CFRT+TMZ group exhibited the highest survival rates among all treatment groups. The eGBM-molGPA, which integrated four clinical and three molecular parameters, stratified patients into low-, intermediate-, and high-risk groups. CFRT+TMZ significantly improved OS compared to HFRT+TMZ or radiotherapy alone in the low-risk (p=0.023) and intermediate-risk groups (p < 0.001). However, in the high-risk group, there was no significant difference in OS between treatment options (p=0.770).

Conclusion CFRT+TMZ may be more effective than HFRT+TMZ or radiotherapy alone for selected eGBM patients. The novel eGBM-molGPA model can guide treatment selection for this patient population.

Key words Glioblastoma, Aged, Radiotherapy, Temozolomide, Graded prognostic assessment, Molecular biomarker

Introduction

Glioblastoma (GBM) is the most aggressive and prevalent primary malignant brain tumor in adults, with incidence increasing with age. The age-adjusted incidence rate of GBM rises dramatically from 1.37 per 100,000 for adults aged 35-44 years to 8.11, 13.19, and 15.17 among those aged 55-64, 65-74, and 75-84 years, respectively [1]. Elderly patients with GBM (eGBM), comprising nearly half of all GBM cases, face a particularly poor prognosis with a median survival of approximately six months [2]. Currently, the standard treatment for GBM involves maximal safe resection followed by temozolomide (TMZ)-based chemoradiation, typically administered as conventionally fractionated radiotherapy (CFRT) at a total dose of 60 Gy in 30 daily fractions [3]. However, applying this regimen to eGBM patients remains controversial due to concerns about tolerance, given their high comorbidities, poor performance status, and increased vulnerability of aged brain tissues to radiation [4,5].

Several randomized trials have compared survival outcomes between CFRT and hypofractionated radiotherapy (HFRT) in eGBM patients, with HFRT delivering a total dose of 34-40 Gy over 2-3 weeks [6,7]. Although these trials demonstrated that HFRT can produce comparable outcomes to CFRT while reducing treatment-related sequelae, they were limited by being conducted in radiotherapy (RT)-alone set-

Correspondence: Chan Woo Wee
Department of Radiation Oncology, Yonsei Cancer Center, Heavy Ion Therapy Research Institute, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: 82-2-2228-8121 E-mail: wcw0108@hanmail.net

Co-correspondence: Hong In Yoon
Department of Radiation Oncology, Yonsei Cancer Center, Heavy Ion Therapy Research Institute, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: 82-2-2228-8110 E-mail: YHI0225@yuhs.ac

*Hye In Lee and Jina Kim contributed equally to this work.

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ting without TMZ administration. More recently, research has established the survival benefit of TMZ-based chemoradiation compared to RT alone in eGBM patients, leading to the widespread adoption of this combination therapy [8,9]. Yet, despite this modern approach for eGBM patients, evidence guiding the choice between CFRT and HFRT in the context of TMZ-based chemoradiation remains scarce, with only retrospective and single-arm prospective studies available [5].

This study hypothesized that a more aggressive approach using CFRT plus TMZ may improve survival outcomes compared to HFRT plus TMZ in selected eGBM patients. We developed a graded prognostic assessment (GPA) model that integrates genomic characteristics of eGBM patients (eGBM-molGPA). Based on this model, we stratified patients into distinct risk groups and evaluated the survival outcomes of CFRT+TMZ, HFRT+TMZ, and RT alone within each group. The primary goal of this study was to provide evidence-based guidance for selecting the most appropriate treatment strategy for individual eGBM patients.

Materials and Methods

1. Study cohort

This multi-institutional retrospective study was conducted across four institutions in Korea (Yonsei Cancer Center, Seoul National University Hospital, Seoul National University Bundang Hospital, and SMG-SNU Boramae Medical Center). We identified elderly patients aged 65 years or older who were newly diagnosed with isocitrate dehydrogenase–wildtype GBM between January 2006 and December 2021. All patients underwent surgical resection or biopsy, followed by RT with or without concurrent and adjuvant TMZ. To ensure an accurate comparison of treatment efficacy between CFRT and HFRT, only patients who completed the planned course of RT were included in the analysis. Additionally, patients who were initially diagnosed with distant metastases or other malignancies, or who were followed up for less than 3 months were excluded.

2. Treatment and follow-up

Treatment and follow-up plan for every patient were developed by a multidisciplinary neuro-oncology team composed of radiation oncologists, neurosurgeons, medical oncologists, radiologists, and neurologists. After preoperative evaluation using magnetic resonance imaging (MRI), patients underwent maximal safe resection of the tumor. The extent of resection was categorized based on postoperative MRI within 48-72 hours as follows: gross total resection was defined as the absence of any enhancing tumor (< 1%); near-total resection as 1-5% residual tumor; subtotal resection as 5%-20%; partial resection as 20%-50%; and biopsy as greater than 50% residual tumor [10,11]. All patients were profiled for methylation of the O^6-methylguanine–DNA methyltransferase (MGMT) promoter, as determined by methylation-specific polymerase chain reaction (PCR). Telomerase reverse transcriptase (TERT) promoter mutations were examined by pyrosequencing via PCR, focusing on C228T and C250T mutations. Next-generation sequencing (NGS) was performed using institution-specific panels: the TruSight Tumor 170 or TruSight Oncology 500 panel at Yonsei Cancer Center, the FIRST brain tumor panel at Seoul National University Hospital, and the Brain v1.0 panel at Seoul National University Bundang Hospital [12-14].

The decision regarding RT dose-fractionation schedules was made by the treating radiation oncologist. Patients treated with a daily dose of 1.8-2.0 Gy and total doses ranging from 59.4 Gy to 70 Gy were classified as receiving CFRT. Conversely, those treated with a daily dose of 2.5-3 Gy and total doses ranging from 39 Gy to 45 Gy were classified as receiving HFRT. During concurrent chemoradiation, TMZ was administered orally once daily at 75 mg/m^2, commencing on the first day of RT and continuing throughout the treatment duration. Following a 4-week break, adjuvant TMZ was administered orally at 150-200 mg/m^2 once daily for five consecutive days every 28 days, for up to six cycles or until disease progression occurred.

Regular follow-up assessments were conducted every 3 months for the first 2 years, and then every 4-6 months thereafter, in accordance with each institution's policy. Tumor progression was defined according to the Response Assessment in the Neuro-Oncology (RANO) Working Group guidelines.

3. Statistical analysis

Overall survival (OS) was calculated from the date of resection to the date of death. Progression-free survival (PFS) was calculated from the date of resection to the date of progression or death. Surviving patients were censored at the last follow-up date. Survival outcomes were estimated using the Kaplan-Meier method. To enhance the robustness of our survival analysis, we extracted individual patient-level 'pseudo-data' from published Kaplan-Meier curves of two landmark randomized trials: the German NOA-08 (NCT01502241) [15,16] and the Nordic trial (ISRCTN81470623) [7], using previously described methodologies [17]. Utilizing these datasets, we reconstructed Kaplan-Meier curves for the respective treatment groups and plotted them alongside the survival curves from our cohort. This approach enabled us to perform an integrated comparison of survival outcomes, including those in the TMZ monotherapy group.

Univariate and multivariate analyses were conducted

Table 1. Patient characteristics

Variable	No. (%) (n=573)
Age (yr)	
Median (range)	71 (65-86)
< 75	446 (77.8)
≥ 75	127 (22.2)
Sex	
Male	315 (55.0)
Female	258 (45.0)
Karnofsky performance scale	
Median (range)	70 (30-100)
90-100	111 (19.4)
70-80	209 (36.5)
≤ 60	253 (44.1)
Charlson comorbidity index	
0-3	262 (45.7)
≥ 4	311 (54.3)
Tumor location	
Frontal	249 (43.4)
Parietal	92 (16.1)
Temporal	178 (31.1)
Occipital	19 (3.3)
Cerebellum	17 (3.0)
Others	18 (3.1)
Subventricular zone involvement	
Group I	138 (24.1)
Group II	145 (25.3)
Group III	158 (27.6)
Group IV	132 (23.0)
Temporalis muscle thickness	
Normal	513 (89.5)
Narrow	60 (10.5)
Extent of resection	
GTR	289 (50.4)
NTR/STR	150 (26.2)
PR/Biopsy	134 (23.4)
Radiotherapy regimen	
CFRT (59.4-70 Gy)	334 (58.3)
HFRT (39-45 Gy)	239 (41.7)
Chemotherapy	
Temozolomide	491 (85.7)
No temozolomide	82 (14.3)
MGMT promotor status	
Methylated	228 (39.8)
Unmethylated	345 (60.2)
EGFR status[a]	
Amplified	86 (31.3)
Non-amplified	189 (68.7)
CDKN2A/B deletion[a]	
Yes	29 (10.6)
No	246 (89.4)
PTEN deletion[a]	
Yes	87 (31.6)
No	188 (68.4)
ATRX status[a]	
Mutated	6 (2.2)
Wild type	269 (97.8)
TERT promoter status[a]	
Mutated	152 (44.7)
Wild type	123 (55.3)
TP53 status[a]	
Mutated	94 (34.2)
Wild type	181 (65.8)
Chromosome 7 gain/10 loss[a]	
Yes	8 (2.9)
No	266 (97.1)

ATRX, alpha-thalassemia/mental retardation X-linked; CFRT, conventionally fractionated radiotherapy; CKDN2A/B, cyclin-dependent kinase inhibitor 2A/2B; EGFR, epidermal growth factor receptor; GTR, gross total resection; HFRT, hypofractionated radiotherapy; MGMT, O-6-methylguanine-DNA methyltransferase; NTR, near-total resection; PR, partial resection; PTEN, phosphatase and tensin homologue; STR, subtotal resection; TERT, telomerase reverse transcriptase; TP53, tumor protein 53. [a]Only in patients with available next-generation sequencing data (n=275).

using a Cox proportional hazards model. Clinical variables included Karnofsky performance scale (KPS) score, Charlson comorbidity index, subventricular zone (SVZ) involvement, temporalis muscle thickness (TMT), and surgical extent. Two radiation oncologists (H.I.L. and J.K.) measured TMT on preoperative contrast-enhanced T1-weighted MRI, following Furtner et al.'s methodology [18]. Patients were classified as having narrow or normal TMT status based on sex-specific mean TMT cut-off values (narrow: ≤ 6.3 mm for men, ≤ 5.2 mm for women; normal: > 6.3 mm for men, > 5.2 mm for women). For patients with available NGS data, we collected molecular profiles for epidermal growth factor receptor, cyclin-dependent kinase inhibitor 2A/2B, phosphatase and tensin homologue, α-thalassemia/mental retardation syndrome X-linked, TERT, and tumor protein p53 (TP53), as well as chromosomal arms 7 and 10. Based on these variables, we performed univariate and multivariate analyses and identified significant prognostic factors associated with OS. We then developed the eGBM-molGPA by assigning scores of 0, 0.5, and 1.0 proportional to the corresponding hazard ratio (HR) in the multivariable model, categorizing patients into three risk groups. All statistical analyses were performed using STATA software ver. 15.1 (StataCorp LP).

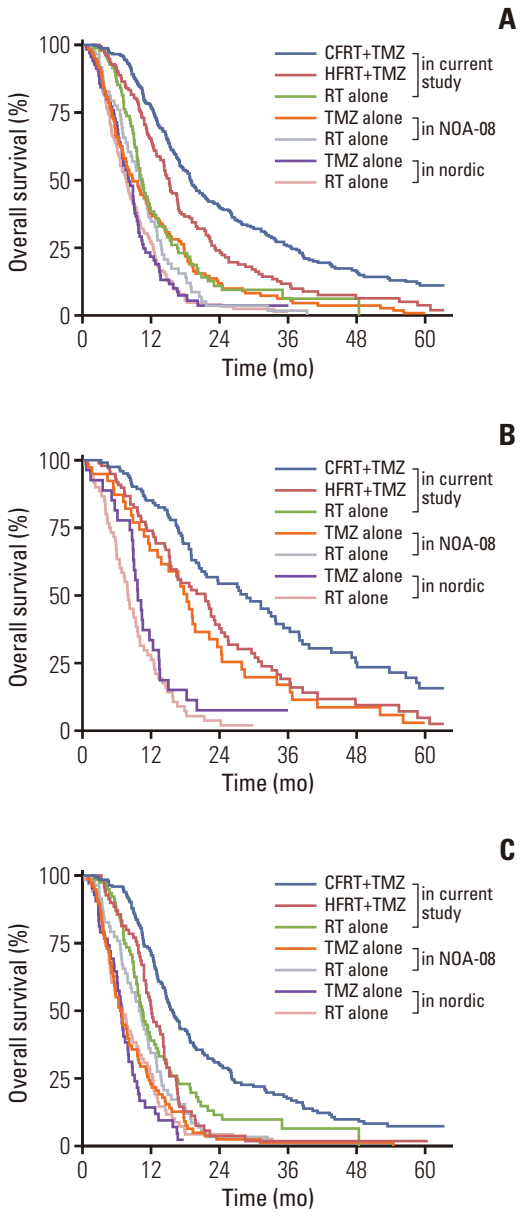

Fig. 1. Kaplan-Meier curves of overall survival by treatment group in the current study, NOA-08, and Nordic trials. Data from the NOA-08 and Nordic trials were reconstructed using individual patient-level pseudodata extracted from published Kaplan-Meier curves. (A) All patients. (B) Patients with a methylated O^6-methylguanine–DNA methyltransferase (MGMT) promoter. (C) Patients with an unmethylated MGMT promoter. CFRT, conventionally fractionated radiotherapy; HFRT, hypofractionated radiotherapy; RT, radiotherapy; TMZ, temozolomide.

Results

1. Patient and treatment characteristics

Patient characteristics are summarized in Table 1. A total of 573 patients with eGBM were included in this study. The median age was 71 years (range, 65 to 86 years), and 22.2% of the patients were older than 75 years. Most patients underwent TMZ-based chemoradiation (n=491, 85.7%), of whom 328 (57.2%) received CFRT+TMZ and 163 (28.4%) received HFRT+TMZ. The remaining 82 patients (14.3%) received RT alone. The median total RT dose was 60 Gy (range, 59.4 to 70 Gy) for the CFRT+TMZ group, 45 Gy (range, 39 to 45 Gy) for the HFRT+TMZ group, and 45 Gy (range, 39 to 60 Gy) for the RT alone group. Molecular profiling revealed that 228 patients (39.8%) had methylation of the MGMT promoter. NGS data were available for 275 patients (48.0%). Of these, 152 (44.7%) had TERT promoter mutations and 94 (34.2%) had TP53 mutations.

2. Survival outcomes and prognostic factors

The median follow-up period was 12.3 months (range, 1.4 to 149.9 months) for all patients and 17.4 months (range, 3.3 to 149.9 months) for survivors. In patients treated with CFRT+TMZ, the median OS was 18.7 months, and 1- and 3-year OS rates were 77.1% and 25.5%, respectively. Patients treated with HFRT+TMZ had significantly lower survival outcomes, with a median OS of 15.1 months, and 1- and 3-year OS rates of 64.9% and 11.5%, respectively (CFRT+TMZ vs. HFRT+TMZ: HR, 1.52; $p < 0.001$). Patients treated with RT alone had the lowest survival outcomes, with a median OS of 10.4 months, and 1- and 3-year OS rates of 38.4% and 6.2%, respectively (CFRT+TMZ vs. RT alone: HR, 2.52; $p < 0.001$ and HFRT+TMZ vs. RT alone: HR, 1.64; p=0.001). PFS was highest in the CFRT+TMZ group, with a median PFS of 12.3 months, followed by the HFRT+TMZ group with a median PFS of 8.5 months, and the RT alone group with a median PFS of 8.0 months (CFRT+TMZ vs. HFRT+TMZ: HR, 1.17; $p < 0.001$; CFRT+TMZ vs. RT alone: HR, 1.82; $p < 0.001$; HFRT+TMZ vs. RT alone: HR, 1.24; p=0.129). Fig. 1 presents the combined survival curves by treatment group in the current study, as well as survival estimates from the NOA-08 and Nordic trials. Notably, regardless of MGMT promoter status, the CFRT+TMZ group in our cohort demonstrated the highest survival rate among all treatment groups across the three studies.

The univariate and multivariate Cox proportional hazard models for OS are presented in Table 2. In the multivariate analysis, the survival benefits of CFRT (p=0.013) and TMZ ($p < 0.001$) remained significant after adjusting for all clinical factors. KPS, surgical extent, and MGMT promoter status were identified as strong prognostic factors, with estimated

Table 2. Univariate and multivariate analysis for overall survival

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (≥ 75 yr vs. < 75 yr)	1.52	1.22-1.90	< 0.001	1.06	0.82-1.36	0.679
Sex (male vs. female)	1.09	0.90-1.32	0.365	-	-	-
Karnofsky performance scale (≤ 60 vs. 70-100)	1.92	1.60-2.32	< 0.001	1.70	1.37-2.10	< 0.001
Charlson comorbidity index (≥ 4 vs. 0-3)	1.38	1.14-1.67	0.001	-	-	-
Subventricular zone involvement (yes vs. no)	1.44	1.19-1.74	< 0.001	1.32	1.09-1.61	0.005
Temporalis muscle thickness (narrow vs. normal)	1.55	1.16-2.08	0.003	1.35	1.05-1.84	0.040
Surgery (NTR/STR vs. GTR)	1.32	1.31-2.09	< 0.001	1.42	1.12-1.79	0.004
Surgery (PR/biopsy vs. GTR)	1.66	1.42-2.07	< 0.001	1.68	1.31-2.15	< 0.001
Radiotherapy regimen (HFRT vs. CFRT)	1.71	1.42-2.07	< 0.001	1.42	1.03-1.95	0.013
Temozolomide (no vs. yes)	2.19	1.69-2.84	< 0.001	1.99	1.49-2.65	< 0.001
MGMT promoter status (unmethylated vs. methylated)	1.88	1.54-2.29	< 0.001	1.87	1.49-2.34	< 0.001
EGFR status (amplified vs. non-amplified)	0.88	0.66-1.17	0.385	-	-	-
CDKN2A/B deletion (yes vs. no)	0.94	0.60-1.47	0.772	-	-	-
PTEN deletion (yes vs. no)	1.08	0.82-1.42	0.588	-	-	-
ATRX status (mutated vs. wild type)	1.83	0.76-4.43	0.180	-	-	-
TERT promoter status (mutated vs. wild type)	1.35	0.94-1.92	0.105	1.41	1.01-1.97	0.040
TP53 status (mutated vs. wild type)	1.34	1.03-1.74	0.030	1.40	1.01-1.95	0.044
Chromosome 7 gain/10 loss (yes vs. no)	0.85	0.27-2.64	0.775	-	-	-

Significant when p-value estimated by multivariate analysis was less than 0.05. ATRX, alpha-thalassemia/mental retardation X-linked; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/2B; CFRT, conventionally fractionated radiotherapy; CI, confidence interval; EGFR, epidermal growth factor receptor; GTR, gross total resection; HFRT, hypofractionated radiotherapy; HR, hazard ratio; MGMT, O-6-methylguanine-DNA methyltransferase; NTR, near-total resection; PR, partial resection; PTEN, phosphatase and tensin homologue; STR, subtotal resection; TERT, telomerase reverse transcriptase; TP53, tumor protein 53.

Table 3. Definition of the eGBM-molGPA and worksheet for total score calculation

Prognostic factor	eGBM-molGPA scoring criteria			Patient score[a]
	0	0.5	1.0	
KPS	≤ 60		70-100	-
Surgery	PR/biopsy	NTR/STR	GTR	-
MGMT promoter status	Unmethylated		Methylated	-
SVZ involvement	Invasion	No invasion		-
Temporalis muscle thickness	Narrow	Normal		-
Gene status	*TERT* mutant or *TP53* mutant	*TERT* wt/unk and *TP53* wt/unk		-
			Total	-

eGBM-molGPA, a molecular graded prognostic assessment for elderly glioblastoma; GTR, gross total resection; KPS, Karnofsky performance scale; MGMT, O-6-methylguanine-DNA methyltransferase; NTR, near-total resection; PR, partial resection; STR, subtotal resection; SVZ, subventricular zone; TERT, telomerase reverse transcriptase; TP53, tumor protein 53; unk, unknown; wt, wild type. [a]Evaluating clinician completes this column.

HRs greater than 1.5 and p-values less than 0.001. Additionally, SVZ involvement, TMT, TERT promoter status, and TP53 status were identified as secondary prognostic factors, demonstrating estimated HRs between 1.3 and 1.5, with p-values ranging from 0.005 to 0.05.

3. GPA for elderly glioblastoma patients

Table 3 details the scoring criteria and elements of the eGBM-molGPA, along with a worksheet for calculating the total score. The three most significant factors (KPS, surgical extent, and MGMT promoter status) were assigned scores of 0 and 1.0 in the eGBM-molGPA. Secondary significant fac-

Table 4. Distribution of eGBM-molGPA scores

Risk group	No. (%)	Median OS (IQR)	p-value
Low risk (total score 3.0-4.5)	154 (26.9)	24 (15-41)	Reference
Intermediate risk (total score 1.5-2.5)	344 (60.0)	16 (11-26)	< 0.001
High risk (total score 0.0-1.0)	75 (13.1)	10 (7-13)	< 0.001

Median survival is in months from the date of surgery (Kaplan-Meier estimate). eGBM-molGPA, a molecular graded prognostic assessment for elderly glioblastoma; IQR, interquartile range; OS, overall survival.

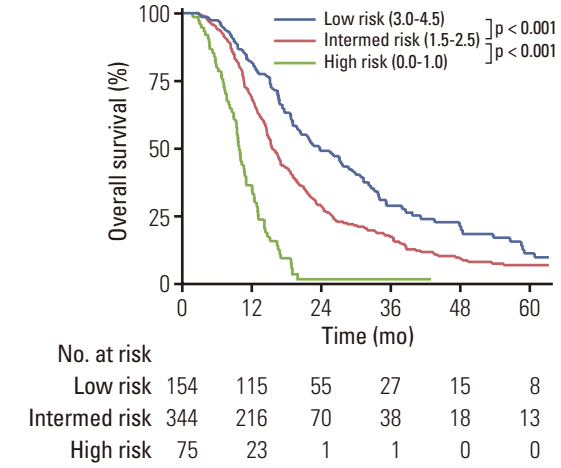

Fig. 2. Kaplan-Meier curves of overall survival by molecular graded prognostic assessment for elderly glioblastoma (eGBM-molGPA) group.

tors (SVZ involvement, TMT, TERT promoter status, and TP53 status) were assigned scores of 0 and 0.5. We categorized total scores into three risk groups: high (0.0-1.0), intermediate (1.5-2.5), and low (3.0-4.5). Survival outcomes for these risk groups are shown in Table 4 and Fig. 2. The median OS was 10, 16, and 24 months in the high-, intermediate-, and low-risk groups, respectively. All adjacent groups in this model demonstrated significantly different hazard functions ($p < 0.001$ for high- vs. intermediate-, high- vs. low-, and intermediate- vs. low-risk groups).

We then compared survival outcomes among treatment options within each risk group (Fig. 3, S1 Table). In the low- and intermediate-risk groups, CFRT+TMZ resulted in significantly higher OS compared to HFRT+TMZ or RT alone. For the low-risk group, the median OS was 27.7 months with CFRT+TMZ versus 18.7 months with HFRT+TMZ (p=0.023), while data for RT alone was unavailable. In the intermediate-risk group, the median OS was 17.5 months for CFRT+TMZ, 15.2 months for HFRT+TMZ, and 11.7 months for RT alone ($p < 0.001$). However, the high-risk group showed no significant OS differences among treatment options, with the median OS of 10.7 months for both CFRT+TMZ and HFRT+TMZ, and 9.4 months for RT alone (p=0.770).

Discussion

In this multi-institutional study, we analyzed treatment outcomes of different adjuvant regimens in eGBM patients. We found that CFRT+TMZ outperformed HFRT+TMZ or RT alone in both the current cohort and the combined cohort including two randomized trials. To identify suitable candidates for this aggressive treatment approach, we developed a novel eGBM-molGPA model incorporating KPS, surgical extent, MGMT promoter status, SVZ involvement, TMT, TERT promoter status, and TP53 status. This model revealed that CFRT+TMZ provided significant OS benefits to patients in the low- and intermediate-risk groups, but not in the high-risk group. The strength of our study lies in its comprehensive dataset from four participating institutions and two major randomized trials focusing on eGBM patients, providing an unprecedented depth of analysis for this patient subgroup.

The definition of "elderly" in GBM patients lacks consensus, with age cut-offs ranging from 60 to 75 years across studies. Among these, the most commonly used threshold is 65 years, which was adopted in our study. This threshold of 65 years is consistent with major landmark trials, including the NOA-08 and the Nordic trial (both included in our analysis), as well as the study by Perry et al. [7,8,15]. Elderly GBM patients are known to have worse prognoses than younger patients due to reduced treatment tolerance, poorer response to treatment, increased toxicity, and possibly altered tumor biology [2]. Considering that the median age at GBM diagnosis is 64 years, and elderly patients comprise more than half of the GBM population, establishing optimal treatment strategies for this specific subgroup is crucial [1]. However, the absence of standardized protocols has led to varied practice across institutions, highlighting the necessity for robust evidence for eGBM patients.

In this study, the CFRT+TMZ group demonstrated significant improvements in both OS and PFS compared to the HFRT+TMZ and RT alone group. While our reported OS was longer than that observed in the NOA-08 and Nordic trials, this disparity may be attributed to our exclusion of patients with incomplete treatment, a criterion not applied in the other two randomized trials. The optimal dose-fractionation regimen for adjuvant RT in eGBM patients has been contro-

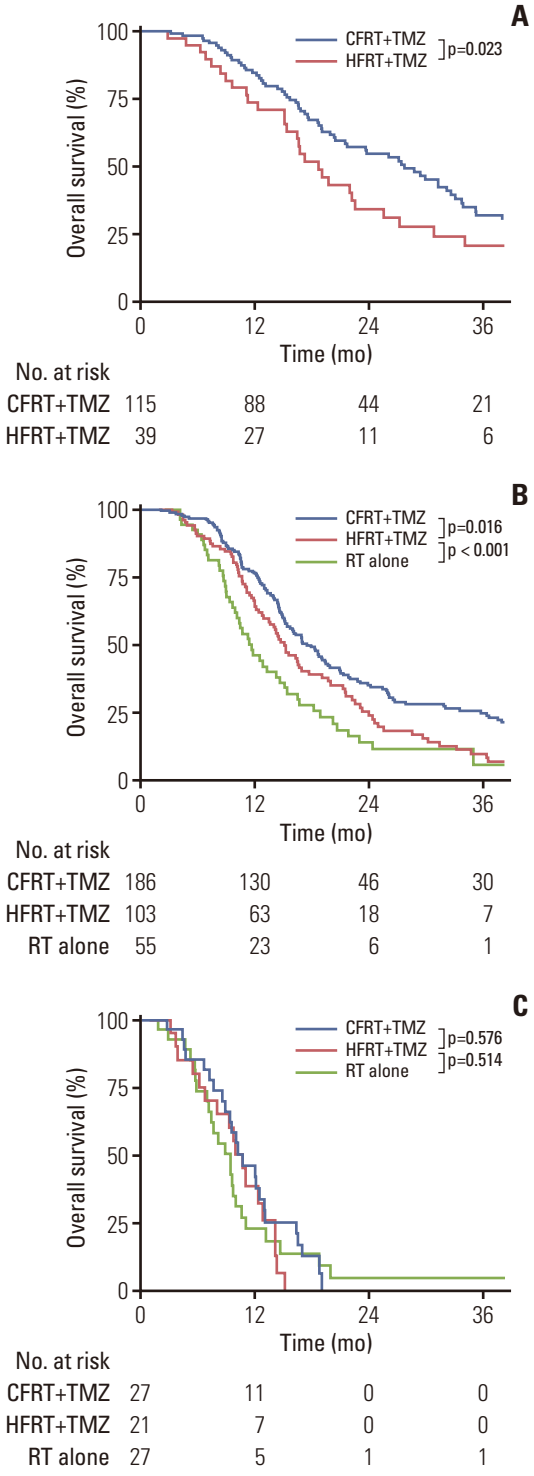

Fig. 3. Kaplan-Meier curves of overall survival by treatment group in molecular graded prognostic assessment for elderly glioblastoma (eGBM-molGPA) risk categories: (A) low-risk group (total score 3.0-4.5), (B) intermediate-risk group (total score 1.5-2.5), and (C) high-risk group (total score 0.0-1.0). CFRT, conventionally fractionated radiotherapy; HFRT, hypofractionated radiotherapy; RT, radiotherapy; TMZ, temozolomide.

versial for the past several decades. Although a Canadian randomized controlled trial found no difference in survival outcomes between CFRT and HFRT [6], other studies have reported encouraging survival outcomes following more aggressive RT strategies in eGBM patients [19]. In a prospective trial involving 32 eGBM patients, Minniti et al. [20] demonstrated that CFRT+TMZ could be a feasible treatment option for this population. Concerns persist regarding higher treatment-related toxicity in MGMT-unmethylated eGBM patients receiving combined modality treatment. However, the findings from the EORTC 26062 study align with our results, indicating improved survival rates with this combined approach regardless of MGMT status [21].

Our analysis identified KPS score, surgical extent, and MGMT promoter status as the strongest prognostic factors, with SVZ involvement, TMT, TERT promoter, and TP53 status as additional prognostic indicators. These findings corroborate numerous previous studies. KPS score, surgical extent, and MGMT promoter status are well-established, robust prognostic factors in GBM patients [22,23]. SVZ involvement and narrow TMT have been recognized as novel prognostic biomarkers for GBM patients in recent years [24,25]. Additionally, *TERT* and *TP53* mutations, frequently detected in GBM patients, have been consistently associated with unfavorable prognosis in previous reports [26,27]. The eGBM-molGPA model proposed in this study incorporated these prognostic factors and demonstrated its clinical utility by effectively stratifying survival outcomes among three risk groups. To our knowledge, this is the first clinically applicable, comprehensive GPA model for eGBM that integrates both clinicopathological and molecular parameters. Furthermore, the eGBM-molGPA model demonstrated that low- and intermediate-risk patients benefited most from CFRT+TMZ, whereas high-risk patients did not derive OS benefit from the treatment approach. It is important to note, however, that the limited number of patients in the high-risk group may have reduced the statistical power of this subgroup analysis. In the intermediate-risk group, CFRT+TMZ showed significant superiority to HFRT+TMZ, although the absolute survival benefit was modest at 2.3 months. Nevertheless, given the poor prognosis associated with eGBM, even such a modest survival gain should not be underestimated [28].

This study has several limitations. First, we did not collect data on treatment-related toxicities, such as hematologic and neurological toxicities, which previous trials identified as factors contributing to the inferiority of CFRT+TMZ compared to HFRT+TMZ or TMZ alone in eGBM patients [29]. Second, our combined analysis incorporated survival data from the current study, the NOA-08 trial, and the Nordic trial. However, the treatment periods differed significantly across these studies. During this time period, advancements

in RT techniques, surgical procedures, brain imaging technologies, molecular marker knowledge, and overall patient care may have influenced treatment outcomes, complicating direct comparisons between studies. These factors should be carefully considered when interpreting the combined results. Despite these limitations, this study represents the largest, multi-institutional cohort focusing on eGBM patients, a subgroup for whom there is a paucity of data in the modern era. We developed a comprehensive model incorporating clinicopathological and molecular parameters, which could guide evidence-based decisions for eGBM patients. Although the eGBM-molGPA model requires further validation, we believe that our robust finding shed light on this promising approach and contribute to establishing optimal treatment strategies for this population.

In conclusion, a more aggressive treatment approach of CFRT+TMZ was associated with improved OS in carefully selected eGBM patients. The novel eGBM-molGPA model can serve as a clinical tool for choosing wisely between treatment regimens. Further prospective studies are warranted to validate our findings and establish the optimal treatment strategies for eGBM patients.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

This study was approved by the institutional review boards of each participating institution (Yonsei Cancer Center IRB No. 4-2022-0126). The requirement for informed consent was waived due to the retrospective nature of the study.

Author Contributions

Conceived and designed the analysis: Kim IA, Lee JH, Wee CW, Yoon HI.
Collected the data: Lee HI, Kim J.
Contributed data or analysis tools: Kim IA, Lee JH, Cho J, Rahman R, Fell G, Wee CW, Yoon HI.
Performed the analysis: Lee HI, Kim J, Rahman R, Fell G, Wee CW.
Wrote the paper: Lee HI, Kim J, Wee CW, Yoon HI.

ORCID iDs

Hye In Lee : https://orcid.org/0000-0003-0839-4086
Jina Kim : https://orcid.org/0000-0001-7173-0324
Chan Woo Wee : https://orcid.org/0000-0002-0631-7549
Hong In Yoon : https://orcid.org/0000-0002-2106-6856

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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