CANCER RESEARCH AND TREATMENT (CRT)

Original Article

To Use or Not to Use: Temozolomide in Elderly Patients with IDH Wild-type MGMT Promoter Unmethylated Glioblastoma Treated with Radiotherapy

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Abstract

Purpose

To identify a specific subgroup of patients among elderly glioblastoma patients aged 70 years or older with unmethylated MGMT promoters (eGBM-unmethylated) who would significantly benefit from the addition of temozolomide (TMZ) to radiotherapy (RT).

Materials and Methods

Newly diagnosed patients with IDH wild-type eGBM-unmethylated treated with RT were included in this multicenter analysis (n=182). RT dose was 45 Gy in 15 fractions (62.3%), 60 Gy in 30 fractions, or 61.2 Gy in 34 fractions. For patients treated with RT plus TMZ (60.4%), TMZ was administered concurrently with RT, followed by six adjuvant cycles. The primary endpoint was overall survival.

Results

During a median follow-up of 11.3 months for survivors, the median survival was 12.2 months. The median survival duration significantly improved with the addition of TMZ to RT compared with that with RT alone (13.6 months vs. 10.5 months, p=0.028). In the multivariable analysis adjusted for clinical, radiological, and genetic biomarkers, the addition of TMZ significantly improved overall survival (hazard ratio, 0.459; p=0.006). In subgroup analysis, median survival was especially improved by 4–5 months in patients with residual disease (p<0.001), Karnofsky Performance Status ≥60 (p=0.033), and age ≤75 years (p=0.090). A significant benefit of TMZ was noted only in patients with two or three of the above factors (median survival, 14.1 months vs. 10.5 months, p=0.014).

Conclusion

The addition of TMZ significantly improved the survival of patients with eGBM-unmethylated treated with RT. The suggested criteria for the specific subgroup in these patients warrant external validation for clinical application.

Keywords Glioblastoma, MGMT, Aged, Temozolomide, Radiotherapy

Introduction

Isocitrate Dehydrogenase (IDH) wild-type glioblastoma (GBM), the most common primary malignant brain tumor in adults [1], demonstrates a dismal prognosis despite current standard treatments, including maximal surgical resection followed by radiotherapy (RT) and temozolomide (TMZ) chemotherapy (RT/TMZ) [2,3]. Although more than half of the patients with GBM are aged 65 years or older, detrimental overall survival (OS) is even shorter in elderly patients [4,5]. The poor prognosis in these elderly patients reflects not only the potential for higher surgical morbidity and the aggressive nature of the disease but also the increased fragility of their brain tissues and general medical condition to tolerate RT and chemotherapy.

A landmark study published nearly two decades ago by Stupp et al. established the current standard for patients aged < 70 years [2]. For these patients, RT/TMZ at 60 Gy in 30 fractions plus concurrent and adjuvant TMZ is recommended. Similarly, in 2017, another landmark trial led by Perry et al. demonstrated that the addition of TMZ to a hypofractionated RT regimen of 40 Gy in 15 fractions in GBM patients aged > 65 years resulted in a statistically significant improvement in OS by approximately 2 months [6]. In both studies, methylation of the O^6-methylguanine-DNA methyltransferase (MGMT) promoter was identified as a predictive biomarker of TMZ efficacy [6,7]. The absolute benefit of TMZ, when added to RT, is a notable 6-month increase in median survival (MS) in both young and elderly patients with methylated MGMT promoters (MGMTp) [6,7]. In contrast, in patients with unmethylated MGMTp, there was only a modest increase in MS at 1–2 months, at the expense of TMZ-related toxicity. The modest increase in survival halts clinicians from using TMZ in addition to RT in elderly patients with GBM with unmethylated MGMTp (eGBM-unmethylated) [8].

The current NCCN guidelines recommend considering hypofractionated RT over 3 weeks or conventionally fractionated RT over 6 weeks, along with concurrent and adjuvant

TMZ, for patients with a Karnofsky Performance Status (KPS) score of 60 or higher, regardless of MGMT methylation status (Category 2A or higher recommendation) [9], and the criteria for recommending TMZ in addition to RT in patients with eGBM-unmethylated remain ambiguous. Therefore, this study aims to identify the subgroup of patients aged 70 years or older with eGBM-unmethylated who would benefit the most from the addition of TMZ to RT.

Methods and Materials

1. Patients

This multicenter study was approved by the Institutional Review Board (IRB) of each participating institution (Severance Hospital IRB No. 4-2022-0126). Patients with newly diagnosed IDH wild-type GBM between 2006 and 2021 from three large tertiary cancer centers in Korea were included. Inclusion criteria were as follows: (1) patients aged 70 years or older at the time of diagnosis; (2) patients with verified wild-type IDH gene and unmethylated MGMTp; and (3) patients treated with RT following surgical resection or biopsy. Patients with a history of another malignancy within the past five years or prior cranial RT/chemotherapy were excluded. Wild-type IDH status was tested by immunohistochemistry using anti-IDH1 R132H (H09) monoclonal antibodies (Dianova, Hamburg, Germany) or by direct sequencing of the IDH1 or IDH2 genes. MGMTp methylation status was determined via pyrosequencing using a cut-off of 8% for the mean percentage of methylated alleles across CpGs 74-80 [10] or methylation-specific PCR. Out of the 182 patients who met the inclusion/exclusion criteria, a subset (n=87, 47.8%) underwent next-generation sequencing (NGS) to assess for *EGFR* amplification, *CDKN2A/B* homozygous deletion, *TERT* promoter mutations, and *TP53* mutations.

2. Surgery, RT, and Temozolomide

Postoperative brain magnetic resonance imaging (MRI) was conducted within 48–72 hours for all surgically treated patients to evaluate the extent of resection. The extent of resection was classified as follows: Gross Total Resection (GTR) signified the complete absence of any enhancing tumor (<1%); near-total resection, characterized by 1–5% residual enhancing tumor; subtotal resection, defined as 5-20% residual enhancing tumor; partial resection, comprising 20-50%; and biopsy was indicated by >50% residual enhancing tumor. The median RT dose was 45 Gy, delivered in 15 fractions. All patients underwent one of three RT dose-fractionation regimens: 60 Gy in 30 fractions, 61.2 Gy in 34 fractions, or the aforementioned 45 Gy in 15 fractions (Table 1).

The adjuvant treatment strategy was determined based on institutional protocols or physician discretion and included either RT alone or in combination with concurrent and adjuvant TMZ (RT/TMZ). TMZ dosing followed the Stupp protocol [2], with up to six cycles administered unless halted owing to confirmed disease progression or unacceptable toxicity. In South Korea, TMZ monotherapy has not been approved for newly diagnosed glioblastomas; thus, it was not analyzed in this study.

Follow-up brain MRI was performed 1-month post-RT and then every 3 months for the first 2 years, with subsequent imaging every 4–6 months in the absence of disease progression or otherwise indicated.

3. Statistical Analysis

The primary endpoint was overall survival (OS), defined as the time from surgery to the date of death or last follow-up. Multivariable analysis using a Cox proportional hazards model (backward stepwise) was conducted to identify the prognostic factors affecting OS. To

evaluate the differences in survival within the subgroups based on TMZ treatment, a log-rank test was performed. Baseline characteristics between the RT/TMZ and RT alone groups were compared using chi-square tests, with statistical significance set at $p<0.05$. All analyses were performed using the IBM SPSS Statistics Version 27 (IBM Corporation, Armonk, NY).

Results

1. Impact of Temozolomide on Overall Survival

The median follow-up duration for survivors was 11.3 months, and the median OS for the entire cohort was 12.2 months (95% confidence interval, 11.0-13.5 months). Among 182 patients, 110 (60.4%) received RT/TMZ, while the remaining 39.6% underwent RT alone. The group treated with RT/TMZ had a higher proportion of patients under 75 years, those with a KPS score of 60 or higher, and those receiving conventional fractionation (60 Gy in 30 fractions or 61.2 Gy in 34 fractions) compared to those receiving RT alone (Table 1). However, the proportion of patients who underwent GTR, a well-recognized prognostic factor, was significantly lower in the RT/TMZ group (Table 1). In a subset of 87 patients who underwent next-generation sequencing (NGS), a higher incidence of CDKN2A/B homozygous deletion and a lower incidence of TERT promoter mutations were observed in the RT/TMZ group.

The inclusion of TMZ in conjunction with RT was associated with a notable enhancement in median OS, extending MS by approximately 3 months in comparison to RT alone (10.5 months vs. 13.6 months, $p=0.028$) (Fig. 1A). This survival benefit persisted as significant even after adjusting for confounding factors in the multivariable analysis, demonstrating TMZ's favorable impact on OS (HR, 0.459; 95% confidence interval, 0.262–0.804; $p=0.006$) (Table 2).

2. Subgroup Analysis

To further identify patient subgroups that would derive the greatest benefit from TMZ, subgroup analyses were conducted based on established prognostic factors. These analyses demonstrated that TMZ conferred a survival advantage in patients aged 75 years or younger (P=0.090), in those with a KPS score of 60 or higher (p=0.033), and in patients with residual enhancing disease post-resection (p<0.001), with a survival extension of 4–5 months observed in these subgroups (Table 3). Consequently, a "TMZ benefit score" was established, categorizing patients based on the presence of 0-1 or 2-3 favorable factors. Patients aged 75 years or younger were included in this category due to the practical consideration that many clinicians are likely to recommend and feel comfortable using TMZ for these patients, despite the marginal statistical significance. Patients with a benefit score of 2-3 (n=130) exhibited a significant improvement in median overall survival (OS) with RT/TMZ compared to RT alone (14.1 months vs. 10.5 months, p=0.014) (Fig. 1B). Conversely, those with a benefit score of 0–1 (n=52) did not show a significant survival benefit with the addition of TMZ (median OS 12.0 months vs. 11.0 months, p=0.882) (Fig 1C).

Discussion

The current study aimed to identify the subset of patients with eGBM-unmethylated aged 70 years or older who would derive a clinically meaningful OS benefit from the addition of concurrent and adjuvant TMZ to RT. In the overall cohort, the addition of TMZ significantly prolonged MS by 3 months in eGBM-unmethylated patients treated with RT, and this significance persisted even after adjusting for various clinical and genetic prognosticators. Patients with two or more factors among residual enhancing disease, KPS 60 or higher, or 75 years or younger (TMZ benefit score ≥2) benefited the most with the addition of TMZ to RT.

Patients with a KPS ≥60 or aged ≤75 years at baseline are more likely to tolerate the additional toxicity of TMZ effectively while benefiting from its antitumor effects. Furthermore, patients with residual disease, a well-acknowledged poor prognostic factor for survival, may derive more benefit from a more aggressive form of adjuvant treatment such as the addition of TMZ to RT compared to those undergoing GTR.

Epigenetic gene silencing of MGMT by promoter methylation, which impairs the ability to remove DNA alkylation caused by TMZ, is a hallmark of the increased efficacy of TMZ in GBM [7]. Although the survival benefit of combining TMZ with RT is much more evident in patients with methylated MGMT, only a modest benefit of TMZ has been demonstrated in landmark clinical trials. Stupp and colleagues reported that in GBM patients aged 70 years or younger with unmethylated MGMT, TMZ reduced the risk of death by 40% and increased the 2-year survival rate from 2% to 15% (p=0.035) [11]. Similarly, in another landmark trial by Perry et al., the addition of TMZ to hypofractionated RT of 40 Gy increased MS by 2 months (p=0.055) in eGBM-unmethylated patients aged 65 years or older [6]. Collectively, a modest survival benefit of TMZ when combined with conventionally fractionated or hypofractionated RT was observed in all age groups with unmethylated MGMTp. In the current study, a modest but significant survival benefit of 3 months was observed.

However, to date, there are no clear criteria recommending the use of TMZ when treating patients with eGBM-unmethylated with RT. In a questionnaire study by the Korean Radiation Oncology Group, the use of TMZ and RT dose fractionation largely varied depending on performance status, age, methylation status of MGMT, and extent of resection [8]. The use of TMZ in patients aged 70 years is mainly dependent on KPS and MGMTp methylation. In patients with unmethylated MGMTp, the use of TMZ decreased from 90% to 50–60 % with

increasing age (68 years → 75 years) and KPS score (90 → 60). Particularly, for an eGBM-unmethylated patient aged 75 years with a KPS score of 60 who underwent non-GTR and would have had a TMZ benefit score of 3, according to our study, 62% of responders answered that they would proceed with RT alone, mostly with hypofractionation. A subgroup of patients with eGBM-umeth who would have significantly benefited from the use of TMZ might have undergone RT alone because of their unmethylated MGMTp and the lack of specific criteria. The development of a comprehensive and accurate definition of the "TMZ benefit subgroup" in patients with eGBM-unmethylated is crucial to adequately treat these patients.

Our study has several limitations, notably its retrospective nature and the potential for selection bias in choosing treatment strategies among RT/TMZ and RT alone, as well as in the selection of RT dose-fractionation schemes. Indeed, the baseline patient characteristics were not well balanced between the RT/TMZ and RT alone groups, as illustrated in Table 1. However, the survival benefit of TMZ was preserved even after adjusting for all possible prognostic factors, as shown in Table 2. One concern is that the vast majority of patients receiving RT alone were treated with hypofractionated RT of 45 Gy in 15 fractions in the current study, whereas more than half of the patients in the RT/TMZ arm received a higher RT dose of 60 Gy in 30 fractions. Although several recent studies have suggested that an increased RT dose of 60 Gy in 30 fractions or 52.5 Gy in 15 fractions, even in patients with GBM, may lead to improved survival outcomes, as referenced in some studies [5,12], the observed MS of 12.2 months in the RT-alone arm in the current study was comparable to or exceeded that reported in several other prospective and retrospective studies involving RT of 60 Gy in 30 fractions and TMZ in elderly patients with GBM [13,14]. Another issue with combining TMZ in patients with eGBM-unmethylated is the sequence of combination of TMZ with RT (concurrent vs. adjuvant) and the optimal cycles of TMZ in the adjuvant setting (6 vs. 12 cycles) [2,6,15,16]. Currently, in

Korea, only concurrent plus adjuvant TMZ of six cycles is approved by the National Health Insurance System for patients with GBM. Another limitation is that toxicity profiles were not reported due to a lack of data.

Moreover, the quantitative results of MGMT promoter testing can significantly influence the response to alkylating agents such as temozolomide (TMZ), not only in IDH wild-type GBM but also in IDH-mutant gliomas [17-21]. Patients in our study were tested for MGMT methylation status using either pyrosequencing (with a cutoff value of ≥8%) or methylation-specific polymerase chain reaction, the two most commonly used methods in clinical practice [19,20]. Although we categorized these patients simply as eGBM-unmethylated, the proportion of methylated CpG sites in the tumor represents a continuous spectrum rather than a binary classification, even though several clinically meaningful cutoff values have been proposed in the literature for GBM [17-21]. Therefore, to provide the best available treatment and avoid futile adjuvant therapy—particularly for GBM patients with MGMT profiles falling into the 'gray zone' of intermediate methylation—further investigation is necessary to identify optimal criteria for administering additional TMZ.

Nevertheless, our study, employing rigorous inclusion and exclusion criteria at some of the Korea's largest brain tumor centers, generates reliable findings from a significant cohort, solely comprising eGBM-unmethylated patients aged 70 years or older. The "TMZ benefit score" proposed in this study is both highly intuitive and convenient for clinical use. Moreover, incorporating next-generation sequencing in patients could provide deeper insights into the molecular mechanisms potentially affecting TMZ's benefits, though this study did not identify any biomarkers to guide TMZ use. Therefore, further investigations with a larger patient cohort and detailed genetic biomarker data are necessary to enhance the precision of these criteria.

In conclusion, this study suggests that TMZ, in addition to RT in eGBM-unmethylated

patients, significantly improves OS, especially in those with residual disease after surgery, those with a KPS score of 60 or higher, or those aged 75 years and younger. Our findings warrant meticulous validation through further studies using external data.

Ethical Statement

This multicenter study was approved by the Institutional Review Board (IRB) of each participating institution (Severance Hospital IRB No. 4-2022-0126).

Author Contributions

Conceived and designed the analysis: Wee CW, Lee JH, Yoon HI, Kim IA.

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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Table 1. Patient characteristics of the MGMT promoter unmethylated elderly radiotherapy cohort (n=182)

Variable	n	(%)	temozolomide (+)		temozolomide (-)		P*
			n	%	n	%	
Total	182	(100.0)	110	(100.0)	72	(100.0)	
Sex							0.346
Male	106	(58.2)	61	(55.5)	45	(62.5)	
Female	76	(41.8)	49	(44.5)	27	(37.5)	
Age (years)							0.044
≤75	129	(70.9)	84	(76.4)	45	(62.5)	
>70	53	(29.1)	26	(23.6)	27	(37.5)	
KPS							0.039
≥60	127	(69.8)	83	(75.5)	44	(61.1)	
<60	55	(30.2)	27	(24.5)	28	(38.9)	
SVZ involvement							0.756
Yes	96	(52.7)	57	(51.8)	39	(54.2)	
No	86	(47.3)	53	(48.2)	33	(45.8)	
Extent of resection							<0.001
GTR	82	(45.1)	38	(34.5)	44	(61.1)	
non-GTR or biopsy	100	(54.9)	72	(65.5)	28	(38.9)	
Radiotherapy							<0.001
Conventional fractionation	67	(36.8)	63	(57.3)	4	(5.6)	
Hypofractionation	115	(63.20)	47	(42.7)	68	(94.4)	
NGS cohort (n=87)							
EGFR amplification							0.7
Present	24	(27.6)	11	(29.7)	13	(26.0)	
Absent	63	(72.4)	26	(70.3)	37	(74.0)	
CDKN2A/B homozygous deletion							0.001
Present	15	(17.2)	12	(32.4)	3	(6.0)	
Absent	72	(82.8)	25	(67.6)	47	(94.0)	
TERT promoter mutation							0.021
Present	50	(57.5)	16	(43.2)	34	(68.0)	
Absent	37	(42.5)	21	(56.8)	16	(32.0)	
TP53 mutation							0.808
Present	27	(31.0)	12	(32.4)	15	(30.0)	
Absent	60	(69.0)	25	(67.6)	35	(70.0)	

*Chi-square test. MGMT, O6-Methylguanine-DNA Methyltransferase; KPS, Karnofsky performance scale; SVZ, subventricular zone; GTR, gross total resection (absence of any T1-enhancing tumor).

Table 2. Multivariable analysis of prognostic factors for overall survival

Variable	HR	95% confidence interval	p
Sex (Male vs. female)	0.889	(0.529 - 1.494)	0.656
Age (≤75 vs. >75)	1.36	(0.821 - 2.252)	0.233
KPS (≥60 vs. <60)	1.546	(0.899 - 2.660)	0.116
SVZ involvement (Yes vs. no)	1.63	(1.009 - 2.634)	0.046
Extent of resection (GTR vs. other)	0.374	(0.224 - 0.624)	<0.001
Temozolomide (Yes vs. no)	0.459	(0.262 - 0.804)	0.006
Radiotherapy (Conventional vs. hypofractionation)	1.258	(0.551 - 2.875)	0.585
EGFR amplification (Present vs. absent)	0.791	(0.453 - 1.381)	0.41
CDKN2A/B homozygous deletion (Present vs. absent)	1.773	(0.913 - 3.443)	0.091
TERT promoter mutation (Present vs. absent)	1.339	(0.787 - 2.277)	0.282
TP53 mutation (Present vs. absent)	1.082	(0.602 - 1.946)	0.792

NGS, next generation sequencing; KPS, Karnofsky performance scale; SVZ, subventricular zone; GTR, gross total resection (absence of any T1-enhancing tumor).

Table 3. Effect of temozolomide on survival in individual subgroups

Variable	Median survival (months)		p*
	temozolomide (+)	temozolomide (-)	
Sex			
Male	13.5	10.5	0.115
Female	14.1	10.4	0.13
Age (years)			
≤75	14.7	10.5	0.09
>70	12.9	10.4	0.573
KPS			
≥60	14.8	11.3	0.033
<60	10.7	9.4	0.732
SVZ involvement			
Yes	12.9	10.2	0.14
No	15.1	11.7	0.173
Extent of resection			
GTR	15.2	12.5	0.276
non-GTR or biopsy	13.2	8.2	<0.001
Radiotherapy			
Conventional fractionation	17	11.4	0.529
Hypofractionation	12	10.4	0.977
EGFR amplification			
Present	13.2	10.5	0.596
Absent	11.2	10	0.286
CDKN2A/B homozygous deletion			
Present	10.7	9	0.502
Absent	12.4	10	0.164
TERT promoter mutation			
Present	10.8	9.6	0.509
Absent	12.2	10.4	0.512
TP53 mutation			
Present	11.2	10.4	0.367
Absent	11.2	10	0.57

*log-rank test. KPS, Karnofsky performance scale; SVZ, subventricular zone; GTR, gross total resection (absence of any T1-enhancing tumor).

Table 4. Criteria for temozolomide-based chemoradiation

Beneficial factors: residual disease, KPS ≥60, and age ≤75 years				
Criteria	n	Median survival (months)		p*
		temozolomide (+)	temozolomide (-)	
Benefit score 2-3	130	14.1	10.5	0.014
Benefit score 0-1	52	12	11	0.882

*log-rank test.

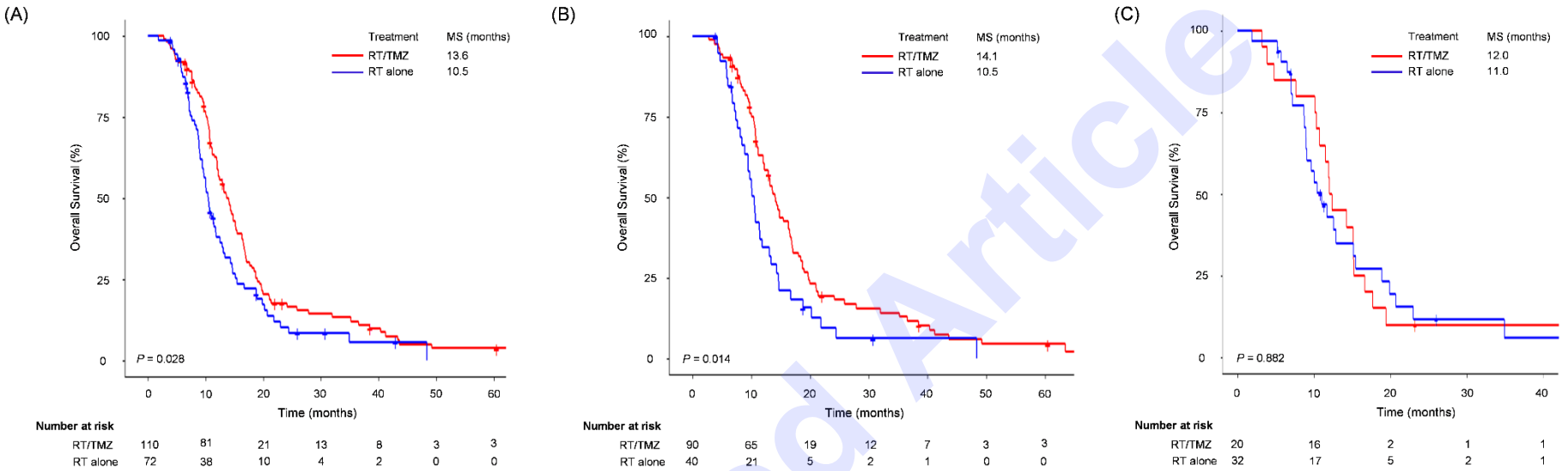

Fig. 1. Kaplan-Meier survival curves of (A) patients treated with radiotherapy plus temozolomide and radiotherapy alone, (B) patients with temozolomide benefit score of 2–3, and (C) patients with temozolomide benefit score of 0–1. RT/TMZ, radiotherapy plus temozolomide; RT alone, radiotherapy alone.