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Extended cycles of adjuvant temozolomide improves survival outcomes in glioblastoma: a retrospective analysis

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Abstract

Aim: Standard treatment includes post-surgical chemoradiotherapy and adjuvant temozolomide (TMZ) for glioblastoma (GBM). There is no consensus on the optimal duration for adjuvant TMZ. This study assessed whether prolonging adjuvant TMZ improved survival outcomes.

Methods: We retrospectively analyzed data of GBM patients who met inclusion criteria at our institute from September 2013 to December 2022. Patients who received 6 cycles of maintenance TMZ constituted the standard group, whereas those who underwent > 6 cycles were classified into the extended group. Kaplan-Meier method was used to estimate the median progression-free survival (PFS) and overall survival (OS). Independent predictors of OS and PFS were explored by Cox regression analyses.

Results: 100 patients were enrolled. Extended adjuvant TMZ significantly improved OS (28.0 *vs.* 10.0 months, $P < 0.001$) and PFS (22.0 *vs.* 8.0 months, $P < 0.001$) in newly diagnosed GBM patients. Subgroup analysis showed that patients with MGMT promoter methylation who received > 6 cycles of adjuvant TMZ experienced a significant increase in OS (34.0 *vs.* 9.0 months, $P < 0.001$) and PFS (26.0 *vs.* 9.0 months, $P = 0.008$). Additionally, in the extended group, patients with MGMT promoter methylation had better survival outcomes compared to

MGMT promoter unmethylated patients (OS: 34.0 *vs.* 17.0 months, $P = 0.013$; PFS: 26.0 *vs.* 12.0 months, $P = 0.025$). In patients with solitary GBM, extended adjuvant TMZ resulted in better OS (11.0 *vs.* 32 months, $P = 0.007$) and PFS (9.0 *vs.* 24.0 months, $P < 0.001$). For patients with multiple GBM, undergoing six or more cycles of adjuvant TMZ did not significantly impact OS ($P = 0.100$) and PFS ($P = 0.067$). The Karnofsky Performance Status (KPS) is employed to assess the health condition of surgical patients. Patients with KPS > 70 exhibited better survival outcomes in the extended group. Nausea and vomiting were the main adverse events reported in both cohorts. However, fatigue emerged as the most severe side effect, specifically within the extended group.

Conclusion: This study indicated that prolonged adjuvant TMZ significantly enhanced OS and PFS in GBM, and the adverse events were acceptable. The benefits were particularly notable in those with MGMT promoter methylation, solitary GBM, and high KPS. The optimal cycles of adjuvant TMZ require large prospective studies to further validate and identify which patient groups benefit the most based on molecular subtyping and clinical characteristics.

Keywords: Glioblastoma, adjuvant temozolomide, MGMT promoter methylation, overall survival

INTRODUCTION

Glioblastoma (GBM) is well-known for its high invasiveness and poor prognosis, representing 50.9% of primary malignant brain tumors and 14.2% of central nervous system tumors[1]. Following maximal safe resection, the standard strategy for GBM includes radiotherapy with concurrent and adjuvant temozolomide (TMZ)[2]. Despite receiving standard treatment, approximately 70% of GBM patients experienced progression within one year, with a five-year survival rate below 5%[3]. The median progression-free survival (PFS) for patients is typically less than 7.0 months, and the median overall survival (OS) generally does not exceed 15.0 months[4]. Tumor Treating Fields (TTFields) are acknowledged as a safe and efficacious adjunct treatment for newly diagnosed GBM[5]. However, its high cost and cumbersome application have limited its adoption in China. Exploring new treatment strategies is essential to address current clinical challenges and improve survival and prognosis for GBM patients. TMZ acts as a DNA alkylating agent that causes DNA double-strand breaks and induces apoptosis of tumor cells. It was typically discontinued after 6 cycles in the standard regimen[6]. In clinical practice, adjuvant TMZ is sometimes extended beyond 6 cycles until tumor progression or patient intolerance occurs, although there is no consensus on this method. Hence, we set out to assess the impact of prolonged adjuvant TMZ on both PFS and OS.

METHODS

Patients

From September 2013 to December 2022, newly diagnosed GBM patients who underwent treatment in the First Affiliated Hospital of Chongqing Medical University were retrospectively analyzed. Inclusion criteria included adults (≥ 18 years) histologically diagnosed with GBM according to the 2021 WHO classification standards, who underwent maximal safe resection, concurrent chemoradiation with TMZ, and at least six adjuvant TMZ cycles with KPS ≥ 60. Exclusion criteria included patients who did not complete the Stupp protocol, with recurrence within six TMZ cycles, postoperative radiation exceeding six weeks, lost to follow-up, or with incomplete clinical data [Figure 1]. Experienced oncology clinical experts reviewed all patient data, including clinical assessments, pathology reports, and radiological results. Approval was granted by the hospital (Approval Number of the Ethics Committee: K2023-047).

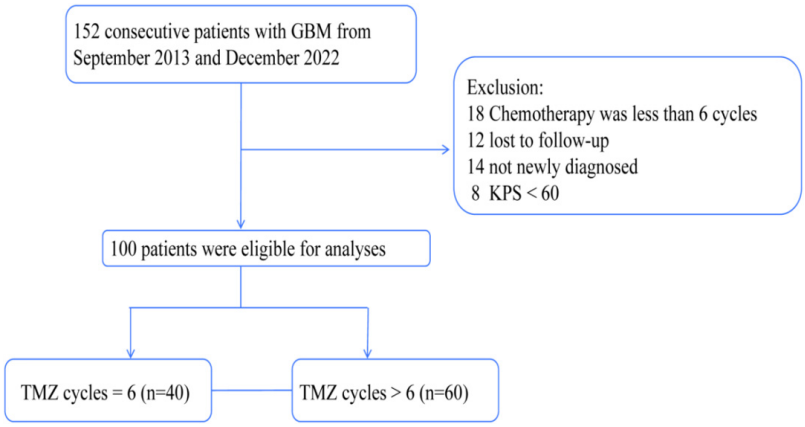

Figure 1. Flowchart of patient inclusion.

Data collection

Data were collected, including age, gender, resection extent, GBM tumor count, KPS, and molecular markers such as O(6) methylguanine-DNA methyl-transferase (MGMT) promoter methylation status, p53, telomerase reverse transcriptase (TERT) promoter mutation, alpha-thalassemia/mental retardation, and the X-linked mutation (ATRX), and Ki-67. Surgeons determined the extent of surgical resection using preoperative and postoperative MRI, along with intraoperative assessments. Gross total resection (GTR) was characterized by the complete absence of any remaining tumor, while near-total resection (NTR) was defined by the removal of over 90% of the tumor. Subtotal resection (STR) indicated a resection rate of 80%-90%, and partial resection (PR) was defined as removing less than 80% of the tumor[7]. The diagnosis date was the date when GBM was histologically confirmed. The date of first recurrence was ascertained either by histological examination or follow-up radiological evaluation.

Treatment

All patients underwent postoperative intensity-modulated radiotherapy (IMRT) at a dose of 60 Gy, administered within 4 weeks following surgery; TMZ (Tasly Diyi Pharmaceutical, Jiangsu, China) at 75 mg/m^2/day was prescribed concurrently during RT for 6 weeks, and then adjuvant TMZ was administrated at a dosage of 150-200 mg/m^2/day for 5 consecutive days every 28 days. Notably, the patient did not receive TMZ before the radiation treatment. Patients who completed 6 cycles of adjuvant TMZ without any disease progression were categorized into the standard group, while those who underwent more than 6 cycles were included in the extended group. In the extended group, the dosage for the first 6 cycles was equivalent to that of the standard group. After completing 6 cycles, each patient's dosage remained the same as in the sixth cycle. After completing standard treatment, patients who showed no disease progression and tolerated the treatment could continue with adjuvant TMZ. The decision to extend adjuvant TMZ was based on a detailed assessment of clinical performance and tumor response, as decided by the patient, their family, and oncologists.

Follow-up schedule

In this study, MRIs were conducted every three months to assess disease progression following 6 cycles of adjuvant TMZ. As required, additional multimodal MRI or PET/CT scans assessed patient tumor burden and differentiated between pseudoprogression and radiation necrosis. OS was defined as the period from initial diagnosis to death or last follow-up, while PFS was calculated from initial diagnosis to MRI-determined disease progression or death, whichever came first.

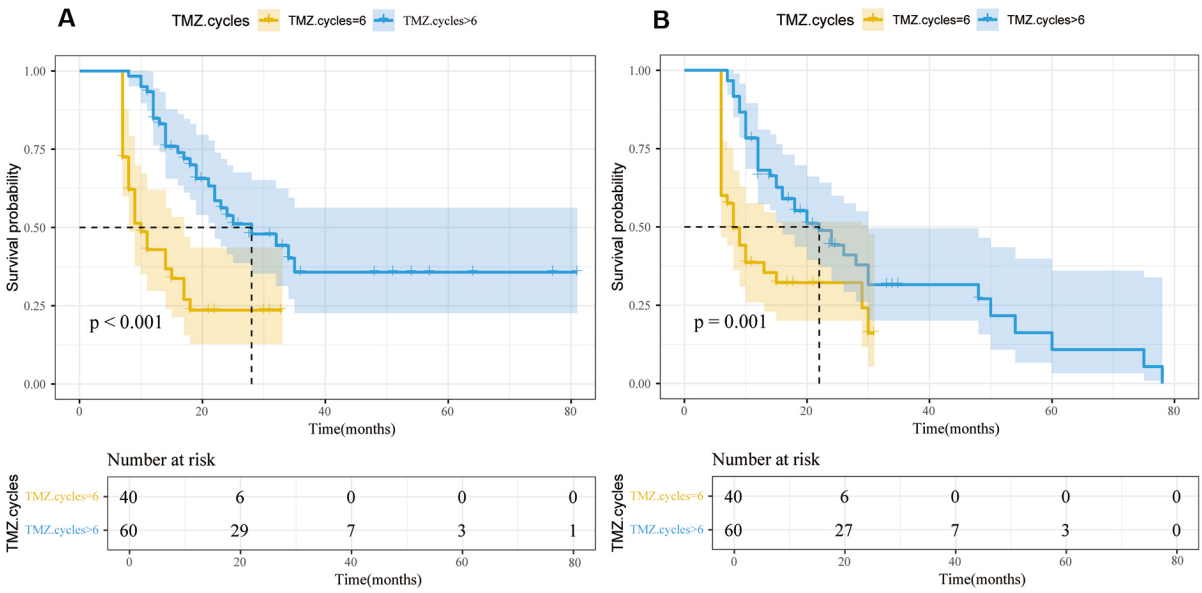

Figure 2. OS (A) and PFS (B) of all patients in the treatment group.

Statistical analysis

Statistical analyses were performed with SPSS 26.0 and R 4.3.2. Variables were analyzed using chi-squared or Fisher's exact test. The receiver operating characteristic (ROC) curves were utilized to determine the optimal cutoff values for the variables. The Kaplan-Meier survival curves were used for analyzing the median PFS and OS. Independent predictors of OS and PFS were explored using the Cox regression model. $P < 0.05$ was statistically significant.

RESULTS

This study included 100 GBM patients in total. Their basic characteristics are summarized in Table 1. ROC curves calculated the optimal cutoff values for age and Ki-67 at 60 years and 35%, respectively. In the extended group, the median cycles of adjuvant TMZ was 8 (7-24), with most patients (32, 53.3%) receiving at least 12 cycles. Patient distribution by TMZ cycles was as follows: 7 cycles - 5 (8.3%), 8 cycles - 8 (13.3%), 9 cycles - 5 (8.3%), 10 cycles - 10 (11.7%), 11 cycles - 3 (5.0%), 12 cycles - 20 (33.3%), and more than 12 cycles - 12 (20.0%).

We first evaluated the impact of extended maintenance TMZ on median OS and PFS in GBM patients. Compared with the standard group, the median OS and PFS of patients in the extended group were significantly longer. The median OS was 10.0 months [95% confidence interval (CI): 7.53-12.47] for the standard group versus 28.0 months (95%CI: 16.99-39.01) for the extended group ($P < 0.001$). The median PFS for the standard group was 8.0 months (95%CI: 5.67-10.33), compared to 22.0 months (95%CI: 14.73-29.27) for the extended group ($P < 0.001$) [Figure 2A and B].

Subgroup analysis based on MGMT promoter methylation status revealed that patients with MGMT promoter methylation who received more than 6 cycles of adjuvant TMZ had longer OS and PFS [Figure 3A and B]. In the standard group, patients with MGMT promoter methylation had a median OS of only 9.0 months (95%CI: 7.10-10.90) and a median PFS of 10.0 months (95%CI: 5.43-14.57), whereas in the extended group, patients with MGMT promoter methylation had a median OS of 34.0 months (95%CI: 26.26-41.74) ($P < 0.001$) and a median PFS of 26.0 months (95%CI: 19.17-32.83) ($P = 0.008$). In the

Table 1. Summary of patient characteristics

Characteristics	Overall *n* = 100	Standard group (*n*, %) *n* = 40	Extended group (*n*, %) *n* = 60	*P* value
Age(years)				0.6856
≤ 60	71 (71.00)	27 (67.50)	44 (73.33)	
> 60	29 (29.00)	13 (32.50)	16 (26.67)	
Sex				0.9024
male	52 (52.00)	20 (50.00)	32 (53.33)	
female	48 (48.00)	20 (50.00)	28 (46.67)	
Main location				0.5198
frontal	55 (55.00)	22 (55.00)	33 (55.00)	
parietal	17 (17.00)	9 (22.50)	8 (13.33)	
occipital	7 (7.00)	1 (2.50)	6 (10.00)	
temporal	13 (13.00)	6 (15.00)	7 (11.67)	
insular	5 (5.00)	1 (2.50)	4 (6.67)	
other	3 (3.00)	1 (2.50)	2 (3.33)	
KPS				0.0004
60-70	47 (47.00)	28 (70.00)	19 (31.67)	
> 70	53 (53.00)	12 (30.00)	41 (68.33)	
Number of glioma				0.7037
solitary	83 (83.00)	32 (80.00)	51 (85.00)	
multiple	17 (17.00)	8 (20.00)	9 (15.00)	
MGMT methylation				0.1302
No	47 (47.00)	23 (57.50)	24 (40.00)	
Yes	53 (53.00)	17 (42.50)	36 (60.00)	
ATRX mutation				1.0000
No	60 (60.00)	24 (60.00)	36 (60.00)	
Yes	40 (40.00)	16 (40.00)	24 (40.00)	
TERT				0.9594
No	32 (32.00)	13 (32.50)	19 (31.67)	
Yes	44 (44.00)	18 (45.00)	26 (43.33)	
unknown	24 (24.00)	9 (22.50)	15 (25.00)	
TP53				0.1712
Negative	31 (31.00)	16 (40.00)	15 (25.00)	
Positive	69 (69.00)	24 (60.00)	45 (75.00)	
Ki-67				0.8238
≤ 30	70 (70.00)	29 (72.50)	41 (68.33)	
> 30	30 (30.00)	11 (27.50)	19 (31.67)	

extended group, further analysis revealed that MGMT promoter methylated patients who received > 6 cycles of adjuvant TMZ chemotherapy had longer OS and PFS (OS: 34.0 *vs.* 17.0 months, $P = 0.013$; PFS: 26.0 *vs.* 12.0 months, $P = 0.025$) [Figure 4].

For patients with solitary GBM, the extended group demonstrated significant improvements in both PFS (median: 24.0 *vs.* 9.0 months; $P < 0.001$) and OS (median: 32.0 *vs.* 11.0 months; $P = 0.007$) compared to the standard group. Among patients with multiple GBMs, the extended group showed a trend toward improved PFS (median: 15.0 *vs.* 6.0 months; $P = 0.100$) and OS (median: 25.0 *vs.* 9.0 months; $P = 0.067$), although these differences were not statistically significant [Figure 5].

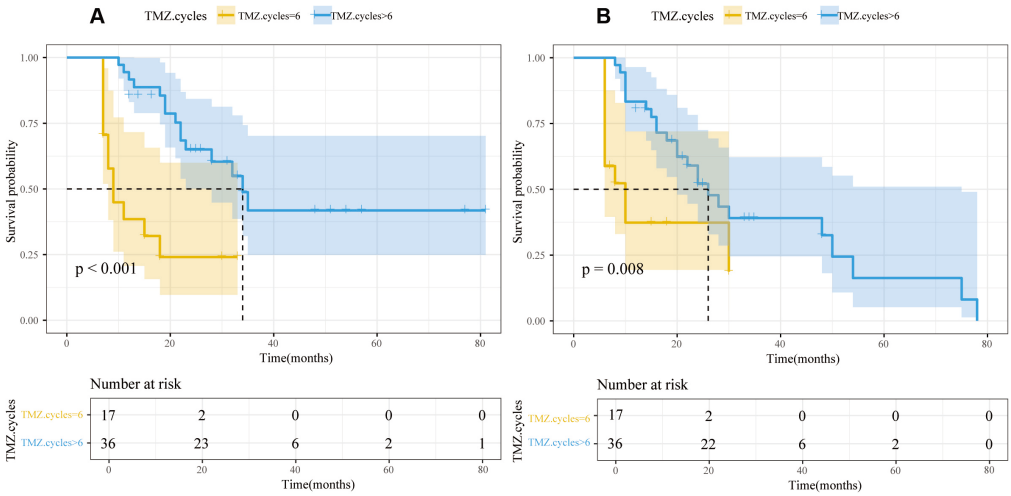

Figure 3. OS (A) and PFS (B) of patients with MGMT promoter methylation in different treatment groups.

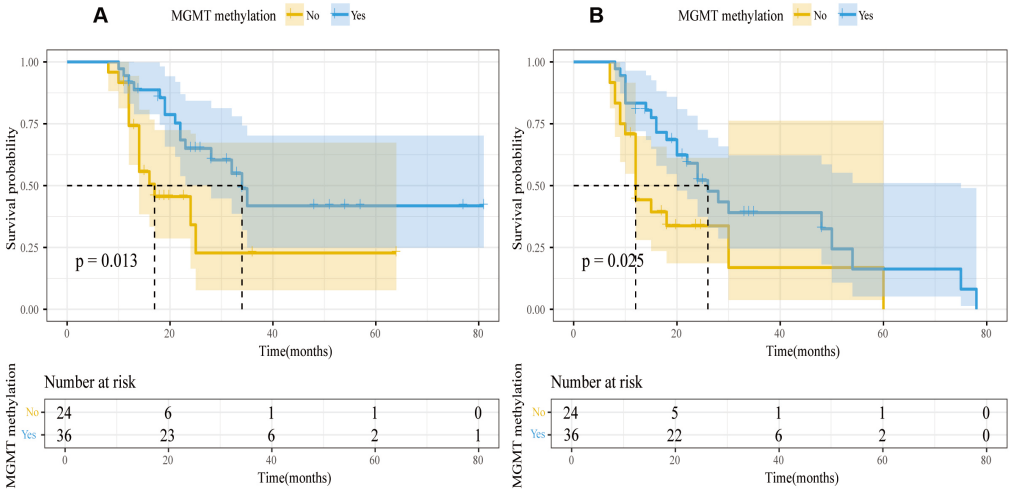

Figure 4. OS (A) and PFS (B) for patients with different MGMT promoter methylation statuses in the extended group.

Patients with KPS < 70 in the extended group experienced longer OS (P = 0.001) and PFS (P < 0.001) compared to those in the standard group [Figure 6]. For patients with KPS> 70, the extended group had longer OS (P = 0.620) and PFS (P = 0.550) than the standard group, though these differences were not statistically significant. Further within-group analysis revealed that patients in the extended group with KPS > 70 had significantly longer OS (P < 0.001) and PFS (P < 0.001) compared to those with KPS < 70 [Figure 7].

Interestingly, the patients who underwent ≥ 12 cycles of adjuvant TMZ demonstrated improved PFS and OS [PFS: 48 months (95%CI: 24.80-71.20); OS was not reached] [Figure 8A and B].

Univariate analysis showed that OS was strongly associated with MGMT promoter methylation status (P = 0.021), KPS (P < 0.001), and the number of adjuvant TMZ cycles (P < 0.001). Our findings also revealed that PFS was related to MGMT promoter methylation status (P = 0.018), KPS (P < 0.001), the number of

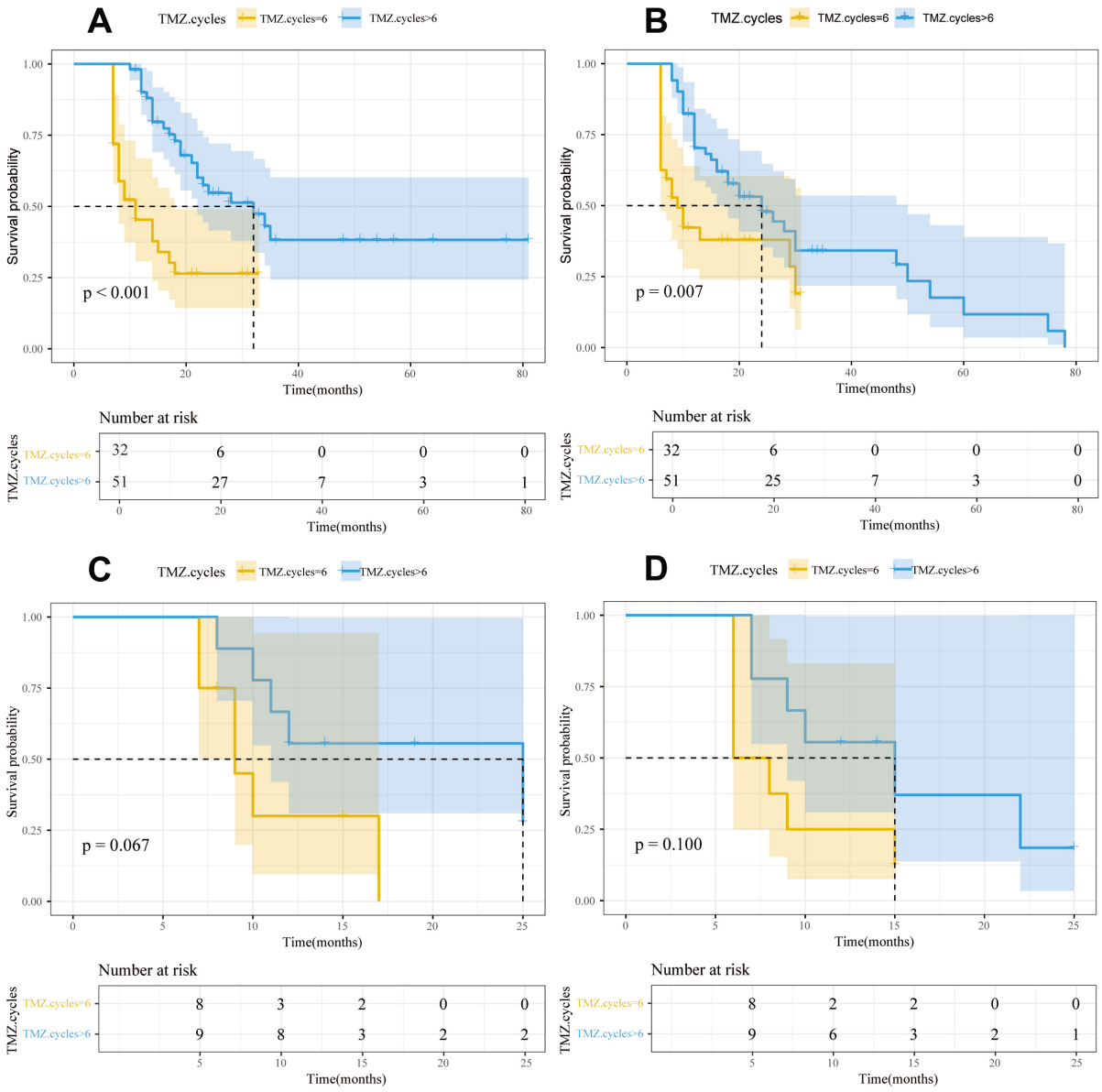

Figure 5. OS (A) and PFS (B) for patients with solitary GBM, and OS (C) and PFS (D) for patients with multiple GBM in the treatment group.

adjuvant TMZ cycles (P = 0.001), and the number of gliomas (P = 0.020). Multivariate Cox analysis indicated that PFS was strongly associated with KPS (P < 0.001) and the number of adjuvant TMZ cycles (P = 0.037), but not with MGMT promoter methylation status (P = 0.832) or the number of gliomas (P = 0.066). OS was significantly associated with KPS (P < 0.001) and the number of adjuvant TMZ cycles (P < 0.001), but not with MGMT promoter methylation status (P = 0.263) [Table 2].

Anemia was the most common grade 3 or 4 toxicity in the standard group, affecting 2 patients (5.0%). Fatigue was most prevalent in the extended group, affecting 6.7% of patients [Table 3]. A small number of patients (0.3%) discontinued the medication due to adverse effects, but there were no medication-related fatalities.

Table 2. Univariate and multivariate Cox analysis for OS and PFS

Characteristics	OS				PFS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P value*	HR (95%CI)	*P value*	HR (95%CI)	*P value*	HR (95%CI)	*P value*
Age (years)								
≤ 60 *vs.* > 60	1.18 (0.65-2.15)	0.588			1.69 (0.99-2.89)	0.052		
Sex								
Male *vs.* female	1.12 (0.67-1.89)	0.660			0.89 (0.54-1.45)	0.630		
Main location	1.06 (0.90-1.25)	0.499			1.00 (0.85-1.18)	0.985		
KPS								
60-70 *vs.* > 70	0.10 (0.05-0.19)	< 0.001	0.10 (0.05-0.19)	< 0.001	0.12 (0.06-0.22)	< 0.001	0.13 (0.07-0.24)	< 0.001
Number of glioma								
Solitary *vs.* multiple	1.90 (0.97-3.71)	0.061			2.10 (1.13-3.93)	0.020	1.84 (0.96-3.52)	0.066
Extent of resection								
GTR *vs.* STR *vs.* NTR	0.78 (0.52-1.17)	0.232			0.90 (0.6-1.35)	0.623		
MGMT promoter methylation								
No *vs.* yes	0.54 (0.32-0.91)	0.021	1.02 (0.58-1.84)	0.924	0.55 (0.34-0.90)	0.018	0.94 (0.56-1.60)	0.832
ATRX mutation								
No *vs.* yes	1.02 (0.59-1.75)	0.949			1.12 (0.67-1.86)	0.667		
TERT								
No *vs.* yes *vs.* unknown	0.99 (0.79-1.25)	0.948			1.09 (0.89-1.3)	0.405		
TP53								
No *vs.* yes	0.62 (0.36-1.07)	0.086			0.74 (0.44-1.24)	0.250		
Ki.67								
≤ 30 *vs.* > 30	0.79 (0.44-1.42)	0.433			0.94 (0.55-1.6)	0.820		
TMZ cycles								
= 6 *vs.* > 6	0.31 (0.18-0.53)	< 0.001	0.32 (0.17-0.57)	< 0.001	0.43 (0.26-0.71)	0.001	0.56 (0.33-0.97)	0.037

Table 3. The incidence of adverse events during adjuvant TMZ

Adverse	The standard group			The extended group			*P* value
Events	All	Grades 1-2	Grades 3-4	All (%)	Grades 1-2	Grades 3-4	
Leukopenia	13 (32.5%)	12 (30.0%)	1 (2.5%)	14 (23.3%)	12 (20%)	2 (3.3%)	0.434
Neutropenia	17 (42.5%)	16 (40.0%)	1 (2.5%)	16 (26.7%)	14 (23.3%)	2 (3.3%)	0.152
Anemia	4 (10.0%)	2 (5.0%)	2 (5.0%)	8 (13. 3%)	5 (8.3%)	3 (5.0%)	0.851
Thrombocytopenia	6 (15.0%)	6 (15.0%)	0	18 (30.0%)	17 (28.3%)	1 (1.7%)	0.138
Fatigue	12 (30.0%)	11 (27.5%)	1 (2.5%)	22 (36.7%)	18 (30.0%)	4 (6.7%)	0.636
Nausea/Vomiting	22 (55.0%)	21 (52.5%)	1 (2.5%)	36 (60.0%)	33 (55.0%)	3 (5.0%)	0.772
Constipation	3 (7.5%)	3 (7.5%)	0	12 (20.0%)	11 (18.3%)	1 (1.7%)	0.153
Pneumonia	8 (20.0%)	8 (20.0%)	0	7 (11.7%)	7 (11.7%)	0	0.391
Hepatotoxicity	2 (5.0%)	2 (5.0%)	0	5 (8.3%)	5 (8.3%)	0	0.810

DISCUSSION

The standard therapeutic regimen for newly diagnosed GBM is far from satisfactory, as 85% of patients experience relapse within two years of treatment[4], leading to significant financial and psychological burdens. Altering treatment strategies is crucial for improving patient prognosis. In 2012, Strik *et al.* began investigating the TMZ dosing regimen for glioma patients, highlighting the potential benefits of dose-dense

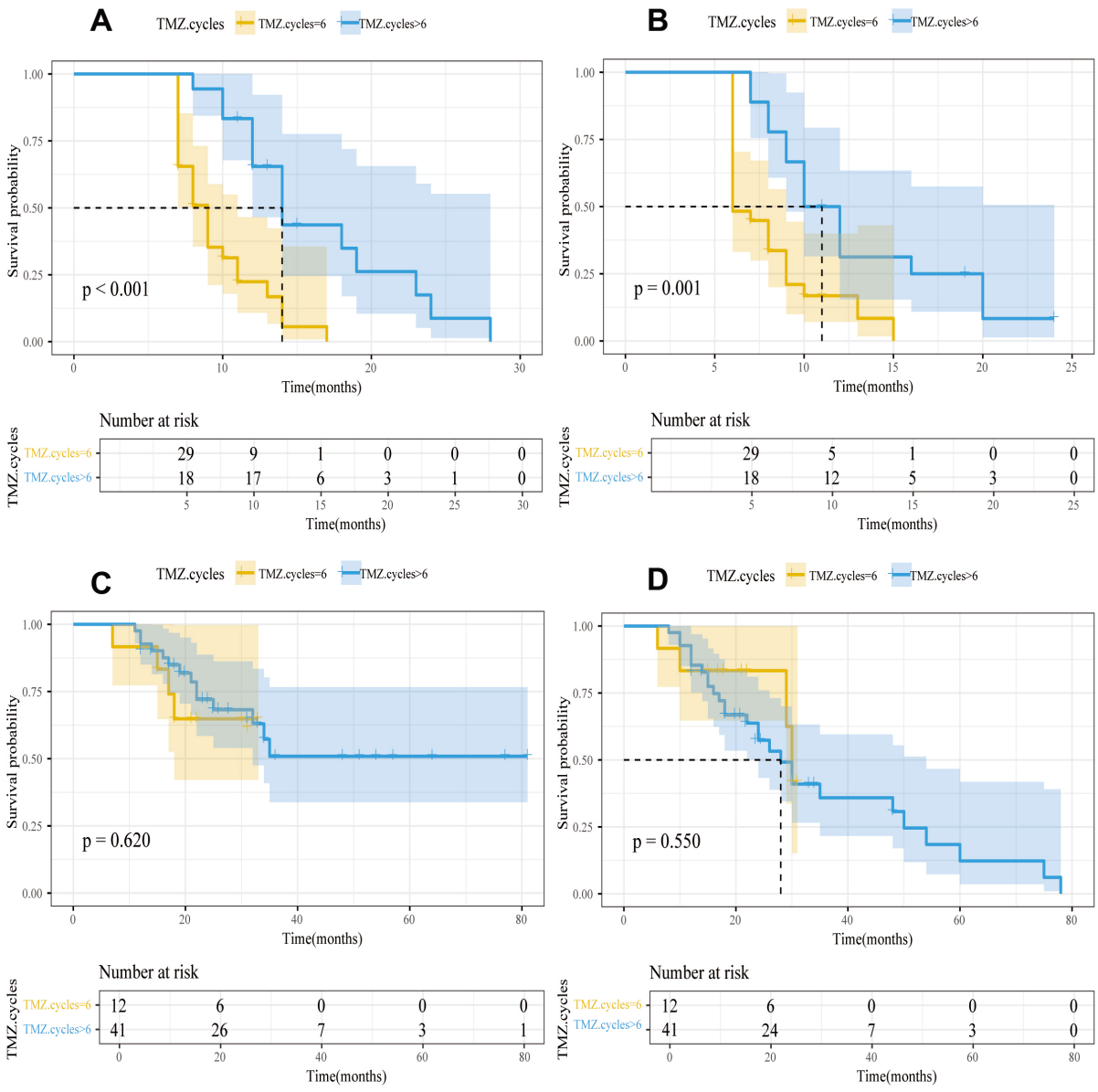

Figure 6. OS (A) and PFS (B) for patients with KPS < 70, and OS (C) and PFS (D) for patients with KPS > 70 in the treatment group.

TMZ regimen[8]. In recent years, experts have shifted their focus to determining the optimal adjuvant chemotherapy cycle for TMZ.

A Phase II trial extended adjuvant TMZ to 7-12 cycles for GBM patients, but the results showed no PFS benefit at 6 months (55.7% for 6 cycles *vs.* 61.3% for more) and increased adverse events[9]. Another study confirmed no significant improvement in 6-month PFS with extended adjuvant TMZ, even in patients with MGMT promoter methylation, where adverse events affected 64% of participants[10]. A secondary analysis showed no OS improvement with prolonged adjuvant TMZ, even in patients with MGMT promoter methylation (HR = 0.89, $P = 0.51$)[11].

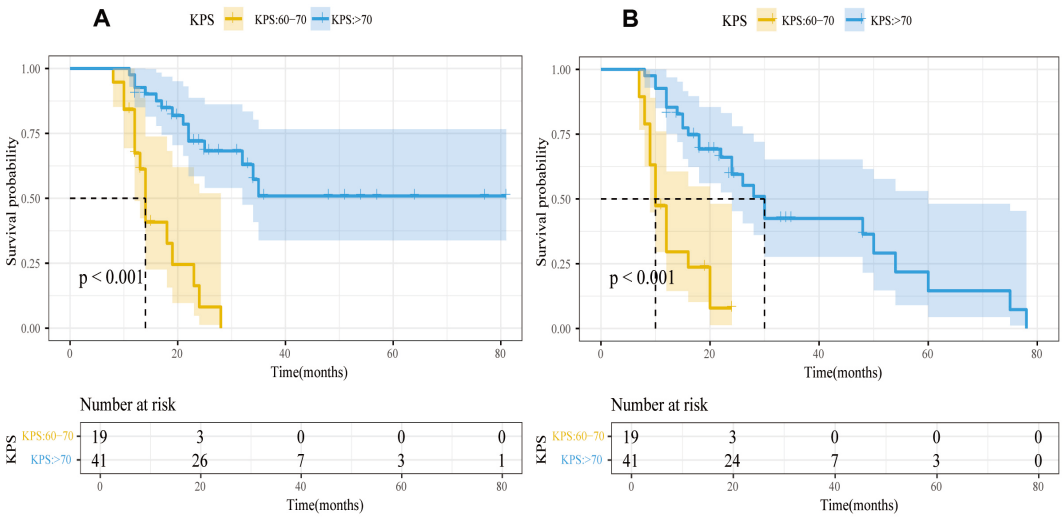

Figure 7. OS (A) and PFS (B) for patients with different KPS in the extended group.

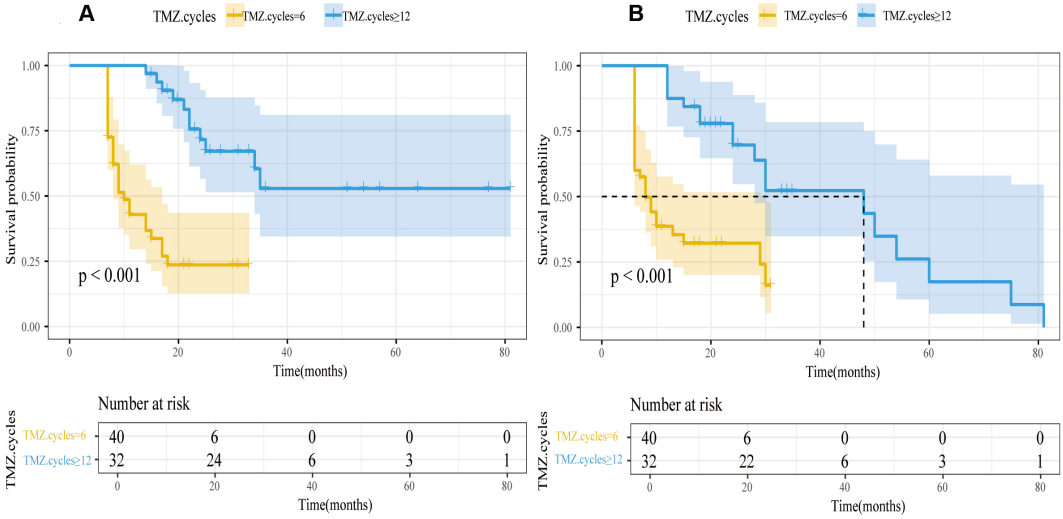

Figure 8. OS (A) and PFS (B) for patients who received ≥ 12 cycles of adjuvant TMZ in the treatment group.

The reported findings in the above-mentioned literature are inconsistent with our data, possibly due to limited sample size, confounding factors, or unrecognized biases. Additionally, PFS is not a reliable endpoint and its clinical significance is questionable, influenced by MRI reporting results and the potential for pseudoprogression. However, other studies indicated that the number of TMZ cycles significantly influenced both PFS and OS[12,13]. This retrospective study of high-grade gliomas included patients who underwent more than 6 cycles of adjuvant TMZ. Psychological assessments revealed no adverse effects, indicating the safety of prolonged TMZ[14]. A recent systematic review and meta-analysis had shown that extended adjuvant TMZ lowered the risk of disease progression (95%CI: 0.60-0.87, P = 0.007) and death (95%CI: 0.57-0.90, P = 0.004) relative to the standard cycles of adjuvant TMZ[15]. A real-world retrospective study involving 422 patients with GBM found that those who received > 6 cycles of adjuvant TMZ had a longer PFS (95%CI: 0.27-0.99, P = 0.048), suggesting that a longer duration of adjuvant TMZ was associated with an extended PFS [3]. Chen found that extended adjuvant TMZ significantly improved the OS (29.00 *vs.*

16.70 months, $P < 0.001$) and PFS (13.80 *vs.* 9.60 months, $P = 0.002$) of newly diagnosed GBM patients compared to standard treatment[16]. According to the literature reviewed, the survival benefit of extended adjuvant TMZ remains a subject of debate. Given the high recurrence rate of GBM and patient concerns about disease recurrence, current clinical practices are focused on assessing the effects of extending adjuvant TMZ on patient survival. In our study, we found that extended adjuvant TMZ improved patient prognosis, with OS increased by 18 months ($P < 0.001$) and PFS increased by 14 months ($P < 0.001$). Table 4 shows the basis of the above-mentioned research information.

We found that patients with MGMT promoter methylation had better survival benefits, and MGMT promoter methylation was a favorable predictor of GBM patients. This was consistent with the results of the pooled analysis of four randomized controlled trials by EORTC and NRG Oncology/RTOG[11]. To confirm the relationship between MGMT promoter methylation and enhanced OS, a Phase III clinical trial categorized GBM patients into standard-dose and dose-dense TMZ treatment groups. The results demonstrated that MGMT promoter methylation significantly improved OS (21.2 *vs.* 14 months; $P < 0.001$) and PFS (8.7 *vs.* 5.7 months; $P < 0.001$)[17]. The study indicated that patients with MGMT promoter methylation experienced significant benefits from prolonged adjuvant TMZ. MGMT functions as a DNA repair enzyme, and MGMT promoter methylation refers to the methylation of the CpG islands in the promoter region of the MGMT gene. When MGMT promoter methylation occurs, the enzyme's ability to effectively repair DNA damage is compromised, thereby enhancing the efficacy of alkylating agents and improving treatment outcomes with TMZ for patients with GBM[18,19]. In clinical practice, extending the adjuvant TMZ may be considered for GBM patients with MGMT promoter methylation.

Clinical observations had noted an increased incidence of multiple GBM, which was associated with shorter survival times and reduced quality of life compared to solitary GBM. Earlier studies have also verified the poorer prognosis associated with multiple GBM[20]. In the largest study to date, involving 7,785 patients with multiple GBM, survival analysis showed that these patients experienced significantly shorter OS compared to those with solitary GBM (12.8 *vs.* 8.3 months, $P < 0.001$)[21]. This could be attributed to the diverse types of lesions, widespread distribution, frequent involvement of deep brain structures, limited surgical resectability, and increased heterogeneity[22]. Our study showed that solitary GBM patients who received extended adjuvant TMZ had survival benefits (OS: 11.0 *vs.* 32 months, $P = 0.007$; PFS: 9.0 *vs.* 24.0 months, $P < 0.001$). Although a beneficial trend was observed in multiple GBM, the survival outcomes did not show a statistically significant difference (OS: $P = 0.100$; PFS: $P = 0.067$). This may be due to small sample sizes or the inherent complexities of multiple GBM, including clinical treatment challenges, limited therapeutic options, and considerable heterogeneity that contributes to treatment resistance. Consequently, prolonged adjuvant TMZ is considered a viable option for both solitary and multiple GBM.

KPS is utilized to evaluate the health status of surgical patients, and the postoperative survival time of glioma patients varies with different KPS. The KPS, an indicator of patient functional status, was recognized as a prognostic factor influencing survival[23]. Liang *et al.* found that KPS below 85 increases mortality risk by a factor of 2.3 (95%CI: 1.141-4.776, $P = 0.020$)[24]. Our findings demonstrated that the KPS independently affected both PFS and OS in patients ($P < 0.001$ for both). For those with KPS < 70, the extended group improved both OS and PFS ($P < 0.001$ for OS, $P = 0.001$ for PFS). However, for patients with KPS > 70, while improvements in OS ($P = 0.620$) and PFS ($P = 0.550$) were noted, these were not statistically significant, potentially due to data bias, a small sample size, or insufficient follow-up. Further analysis of a larger group indicated that patients with higher KPS showed more substantial benefits ($P < 0.001$ for OS and PFS). Therefore, it is recommended that adjuvant TMZ treatment for well-conditioned GBM patients with high KPS be extended in clinical practice.

Table 4. Baseline characteristics of the included analysis

Study	N	OS (months)	*P* value	PFS (months)	*P* value
	TMZ cycles: 6 *vs.* > 6				
Balana *et al.*, 2020[9]	79 *vs.* 80	23.3 *vs.* 18.2	0.16	7.7 *vs.* 9.5	0.95
Gately *et al.*, 2024[10]	101 *vs.* 104	20.1 *vs.* 19.4	0.87	7.8 *vs.* 9.7	0.59
Blumenthal *et al.*, 2017[11]	333 *vs.* 291	24.9 *vs.* 27.0	0.52	10.4 *vs.* 12.2	0.03
Darlix *et al.*, 2013[12]	38 *vs.* 20	84% *vs.* 93% 18 months 65% *vs.* 76% 24 months	NA NA	52.5% *vs.* 73.3% 18 months 25.7% *vs.* 65.9% 24 months	NA NA
Barbagallo *et al.*, 2014[13]	18 *vs.* 19	8.0 *vs.* 28.0	0.0001	4.0 *vs.* 20.0	0.0002
Gupta *et al.*, 2023[15]	1,342 *vs.* 1,236	Risk of death	0.004	Risk of progression	0.007
Chen *et al.*, 2022[16]	40 *vs.* 53	16.7 *vs.* 29.0	0.004	9.6 *vs.* 13.8	0.002

Our study found that although the incidence of toxicity was more common in the extended group, these events were generally tolerable with adjuvant TMZ. No treatment-related deaths occurred, and only 2 (2%) patients discontinued treatment due to toxicity. Consequently, prolonged adjuvant TMZ therapy is deemed safe and tolerable.

The study is a single-center retrospective study, which might result in relative selection bias. Additionally, the limited sample size and the inconsistency in the cycles of adjuvant TMZ could have an impact on the study results. To more accurately determine the optimal duration of adjuvant TMZ, future studies should be prospective, multicenter trials. As TTFields gain clinical use and demonstrate survival benefits, our next step is to explore combining them with extended adjuvant TMZ. Upcoming research will aim to identify the populations that derive the greatest benefits using clinical and molecular markers.

Conclusion

This study indicated that extended adjuvant TMZ improved prognosis in GBM patients, especially those with MGMT promoter methylation, solitary GBM, and high KPS. Despite an increase in adverse events, the regimen was still tolerable. Future prospective clinical trials are essential to explore the optimal cycles of adjuvant TMZ, determine which patient groups derive the most benefit, and evaluate the effects of combining TMZ with other therapies.

DECLARATIONS

Authors' contributions

Contributed to the conception and design of the work, the acquisition and analysis of data, as well as manuscript writing: Xu H
Contributed to the design of the work: Wang C, Hu Y
Contributed to the acquisition and analysis of data: Yu S
Contributed to the analysis and interpretation of data, as well as manuscript writing: Ren Q, Jiang L

Availability of data and materials

The data that support our findings in this study are available from the corresponding author upon reasonable request.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethics approval and consent to participate

The Ethics Committee of Chongqing Medical University approved the study (Approval Number: K2023-047). All participants provided verbal informed consent prior to participation.

Consent for publication

Not applicable.

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