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ORIGINAL ARTICLE

Chemoradiotherapy with temozolomide vs. radiotherapy alone in patients with IDH wild-type and TERT promoter mutation histological grade 2/3 gliomas: An extension retrospective analysis of a randomized controlled trial

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Abstract

Background: Given the poor prognosis of IDH wild-type (IDH-wt) and telomerase reverse transcriptase promoter mutation (TERTp-mut) histological grade 2 to 3 gliomas, the World Health Organization has reclassified it as molecular glioblastoma. However, the effectiveness of chemoradiotherapy (CRT) in these patients remains unclear, especially in comparison to radiotherapy alone (RT). This study aims to assess CRT's efficacy in this population.

Methods: A prospective randomized study was conducted at Beijing Tiantan Hospital from 2016 to 2019, enrolling 37 patients with histologically confirmed grade 2/3 IDH-wt/TERTp-mutant gliomas. Patients were randomly assigned to receive either RT (n = 18) or CRT (n = 19). After preliminary analysis showed a significant overall survival (OS) benefit in the CRT group, the study cohort was expanded from 2020 to 2022 by recruiting an additional 21 patients who all received CRT. Primary endpoints were OS and progression-free survival (PFS).

Results: The final cohort comprised 58 patients (RT, 18; CRT, 40) with a median follow-up of 43.7 months (range, 7.9–75.1). CRT significantly improved OS compared to RT alone, with a median OS of 25.8 versus 17.2 months (hazard ratio, 0.31; 95% CI, 0.16–0.62; p = .001) and 2-year OS rate of 63.0% versus 16.7%. PFS also favored CRT, showing median PFS of 14.2 versus 7.1 months (hazard ratio, 0.38; 95% CI, 0.21–0.70; p = .002) and 1-year PFS rate of 56.6% versus 33.3%. Multivariable analysis confirmed CRT benefits were independent of O6-methylguanine-DNA methyl-transferase (MGMT) status (OS, p = .001; PFS, p = .002). Treatment was well-tolerated with no grade ≥3 toxicities in the CRT group.

Jing Zhang and Peng Wang contributed equally.

Conclusion: CRT significantly improves survival in IDH-wt/TERTp-mut grade 2 to 3 gliomas with favorable safety.

Clinical trial registration: Trial registry name: CCRT With Temozolomide Versus RT Alone in Patients With IDH Wild-type/TERT Promoter Mutation Grade II/III Gliomas. Registration identification number: NCT02766270. URL for the registry: https://clinicaltrials.gov/study/NCT02766270?cond=NCT02766270&rank=1

KEYWORDS
glioma, TERT mutation, IDH wildtype, chemoradiotherapy, radiotherapy

INTRODUCTION

In 2021, the World Health Organization (WHO) introduced a revised version of the molecular pathological grading system for gliomas (WHO CNS 5).[1] A subgroup of IDH-wildtype (wt) diffuse astrocytomas diagnosed histologically as grade 2 to 3, yet possessing molecular features of either telomerase reverse transcriptase promoter mutation (TERTp-mut), and/or the combined pattern of whole chromosome 7 gain and whole chromosome 10 loss (+7/−10), and/or amplification of epidermal growth factor receptor, was reclassified as glioblastoma, IDH-wt, WHO grade 4 (molecular GBM [mGBM]).[2] With outcomes resembling those of histological glioblastoma,[3] the NCCN guidelines recommend treatment using radiotherapy alone (RT) and both concurrent and adjuvant temozolomide (TMZ), which is the standard treatment for newly diagnosed glioblastomas.[4,5] However, no evidence demonstrate the treatment options for IDH-wt gliomas containing molecular glioblastoma features.

In 2016, we conducted research from the CGGA database demonstrating patients with IDH-wt/TERTp-mut lower grade gliomas had a poor outcome.[6] These findings suggest that these patients require more aggressive treatment.[7,8] Accordingly, we conducted a prospective randomized study to examine the efficacy and safety of RT concurrent with TMZ followed by adjuvant TMZ (chemoradiotherapy [CRT]) in patients with grade 2 to 3 IDH-wt and TERTp-mut gliomas (grade 2/3 $G_{IDH\text{-}wt/TERTp\text{-}mut}$). Between September 2016 and December 2019, 37 eligible patients were enrolled and analyzed in the study. Patients were assigned to receive either RT (n = 18) alone or CRT (n = 19). The preliminary results showed that median overall survival (OS) in the CRT and RT-alone groups were statistically different (25 vs. 17 months; p = .017), whereas progression-free survival (PFS) values were not (16 vs. 7 months; p = .840) with 17 months' follow-up.[9] Consequently, on completion of follow-up in 2020, we terminated the trial and published the first set of findings. The preliminary results did not show statistically significant differences in PFS, potentially because of the limited sample size. To address this, we plan to adhere to the original inclusion and exclusion criteria for future studies. Based on ethical considerations and the principle of patient benefit, we subsequently enrolled 21 additional patients into the CRT group and included patients from the earlier prospective study in a unified analysis to further validate the efficacy of chemoradiotherapy for patients with mGBM.

MATERIALS AND METHODS

Patients

Dates of enrollment of expansion patients were from June 2020 to January 2022. All patients were recruited from the Beijing Tiantan Hospital according to inclusion and exclusion criteria from the previously published clinical trial[9]: (1) newly diagnosed supratentorial diffuse glioma of histological grade 2 to 3; (2) patients' molecular pathological profile comprised IDH-wt and TERTp-mut, and the 1p/19q status indicated non-codeletion; (3) age of the patients ranged between 18 and 70 years; and (4) Karnofsky performance scale (KPS) score was ≥60. The Ethics Committee of Beijing Tiantan Hospital approved this study, and all enrolled patients provided signed informed consent.

Pathology assessments

The central pathology laboratory evaluated all samples to determine the histological grade and molecular features. Each sample was assessed by two or more senior pathologists who reached a consensus. Patients were eligible for the study if two neuropathologists histologically confirmed their diagnosis according to the 2016 WHO classification guidelines.[10] When the cell density was less than 2/10 high-power fields, considering the cellular density and nuclear atypia, it will be classified as WHO grade 2; otherwise, it was classified as WHO grade 3.

The mutation status of IDH1 and IDH2 were determined using DNA pyrosequencing next-generation sequencing (NGS). MGMTp methylation status were determined using DNA pyrosequencing, as described previously.[11] Genomic DNA was isolated from formalin-fixed and paraffin-embedded tissue by using the QIAamp DNA FFPE Tissue Kit (Qiagen, Hilden, Germany) and subjected to pyrosequencing (PyroMark Q24 ID System, Qiagen) using the primer 5′-GGATATGTTGGGATAGT-3′ according to the manufacturer's instructions. The methylation values obtained were averaged across the seven CpG loci tested within the O6-methylguanine-DNA methyl-transferase (MGMT) promoter. The samples were considered MGMT promoter methylated with an average methylation >10%. The mutation status of TERT promoter was determined by Sanger sequencing and NGS[6]; 1p/

19q codeletion testing was performed using fluorescence in situ hybridization.[12]

Treatment

Patients who underwent RT received fractionated focal irradiation at a dose of 2 Gy per fraction administered once daily for 5 days per week over a period of 6 weeks, for a total dose of 60 Gy. Concomitant TMZ at a daily dose of 75 mg/m^2 was administered throughout the entire duration of RT. Four weeks after the completion of concomitant radiochemotherapy, the patients received TMZ on days 1 through 5 (150–200 mg/m^2). TMZ treatment was repeated every 28 days for up to 12 courses. (Figure 1). Patients were examined weekly during RT and underwent a full clinical examination, blood hematology, and chemistry test screening before every cycle of chemotherapy. Tumor response and progression were defined according to the Response Assessment in Neuro-Oncology criteria.[13] Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).

Statistical methods

The primary endpoint for the analysis of treatment efficacy was OS; the secondary endpoint was PFS. OS was defined as the time from initial diagnosis to death from any cause, with censoring at the last follow-up for surviving patients. PFS and OS were estimated using the Kaplan–Meier method in GraphPad (version 9.25). Survival rates between the groups were compared using log-rank tests. The distribution of categorical variables in the two groups was tested using the χ^2 test and Fisher exact test; the distribution of continuous variables was assessed through the Mann-Whitney *U* test. Multivariate Cox proportional hazards analysis was used to identify independently prognostic factors for OS and PFS. A p value < .05 was considered statistically significant. The proportional hazards assumption was verified using Schoenfeld residuals. No significant violations were detected (all covariates: $p > .05$).

Because of the limited sample size, conventional statistical tests may lack power to detect baseline imbalances. We evaluated covariate balance between the CRT and RT groups using standardized mean differences (SMD), with an SMD <0.1 indicating good balance. Variables with SMD >0.1 were considered potential confounders and adjusted for in sensitivity analyses. To address residual imbalance, we performed two sensitivity analyses. Propensity score matching: Patients receiving CRT were 1:1 matched to RT patients using nearest-neighbor matching with a caliper width of 0.2 standard deviations of the logit propensity score. Inverse probability of treatment weighting: Weights were derived from propensity scores to create a pseudo-population with balanced covariates. In both approaches, we reestimated hazard ratios (HRs) for PFS/OS using Cox models and compared them with the primary unadjusted analysis.

RESULTS

Clinical characteristics

Between June 2020 and January 2022, 21 eligible patients were enrolled in the study at Beijing Tiantan Hospital. A total of 58 patients (37 original and 21 recruited during the extension) were included in the final analysis. These patients received either RT alone ($n = 18$) or CRT ($n = 40$). The last follow-up date was May 6, 2025. The median follow-up duration was 43.7 months (range, 7.9–75.1 months). The median age was 54.5 years (range, 24–70 years). The median KPS score at randomization was 80 (range, 60–100). Surgery was the primary treatment and was classified as gross total resection (GTR) ($n = 34$) or subtotal resection ($n = 24$). All tumors confirmed by the central pathological review were IDH-wt, 1p/19q non-codeletion, and TERTp-mut; these included 33 patients with grade 3 astrocytoma and 25 patients with grade 2 astrocytoma. The characteristics of the two treatment groups were well-balanced at baseline (Table 1). There were also no

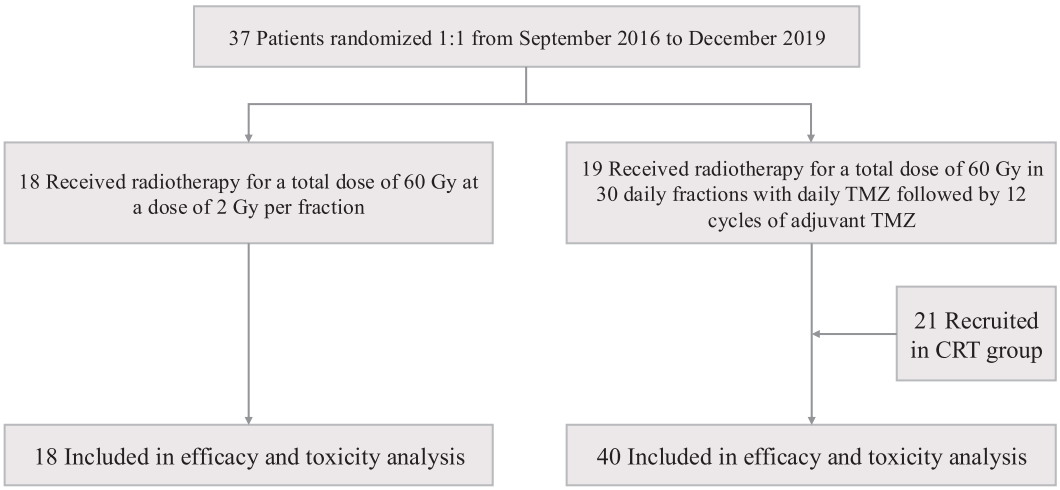

FIGURE 1 Overview of screened and randomly assigned patients. CRT indicates temozolomide plus radiotherapy.

TABLE 1 Comparison of clinical characteristics.

Characteristics	CRT (%)	RT (%)	*p* value[a]
Number	40	18	NA
Age			.158[b]
Median age (range)	54 (24–70)	59.5 (33–68)	
Sex			.471
Male	25 (62.5)	13 (72.2)	
Female	15 (37.5)	5 (27.8)	
Location			.751
Single lobe	24 (60.0)	10 (55.6)	
Multilobe	16 (40.0)	8 (44.4)	
Histology grading			.89
Grade 2	17 (42.5)	8 (44.4)	
Grade 3	23 (57.5)	10 (55.6)	
Resection			.751
GTR	24 (60.0)	10 (55.6)	
STR	16 (40.0)	8 (44.4)	
MGMTp-meth			.664
Yes	18 (45.0)	7 (38.9)	
No	22 (55.0)	11 (61.1)	
Epidermal growth factor receptor-amp			NA
Yes	3 (7.5)		
No	7 (17.5)		
NA	30 (75.0)	18 (100.0)	
+7/−10			NA
Yes	7 (17.5)		
No	3 (7.5)		
NA	30 (75.0)	18 (100.0)	

Abbreviations: CRT, temozolomide plus radiotherapy; GTR, gross total resection; NA, not applicable; RT, radiotherapy alone; STR, subtotal resection.

[a]Chi-square test.

[b]Mann-Whitney *U* test.

statistical differences in baseline characteristics between the previous study patients and those subsequently included (Table 2).

Survival analysis

Of the 58 patients, 41 (70.7%) had died from any cause by the time of the last follow-up. The distribution of deaths was 17 (89.5%) in the RT group and 24 (60.0%) in the CRT group. The vast majority of these fatalities (95.1%) were primarily attributed to disease progression. The 2-year OS rate was 63.0% (95% CI, 49.3–80.6) in the CRT group and 16.7% (95% CI, 5.9–46.8) in the RT-alone group. The 1-year PFS rates

TABLE 2 Comparison of clinical characteristics received CRT treatment.

Characteristics	Previous study (%)	Subsequent patients (%)	*p* value[a]
Number	19	21	NA
Age			.331[b]
Median age (range)	54.5 (24–67)	54.5 (31–70)	
Sex			.683
Male	13 (68.4%)	12 (57.1%)	
Female	6 (31.6%)	9 (42.9%)	
Location			.477
Single lobe	13 (68.4%)	11 (52.4%)	
Multilobe	6 (31.6%)	10 (47.6%)	
Histology grading			1.000
Grade 2	8 (42.1%)	9 (42.9%)	
Grade 3	11 (57.9%)	12 (57.1%)	
Resection			.331[c]
GTR	16 (84.2%)	20 (95.2%)	
STR	3 (15.8%)	1 (4.8%)	
MGMTp-meth			.215
Yes	11 (57.9%)	7 (33.3%)	
No	8 (42.1%)	14 (66.7%)	

Abbreviations: CRT, temozolomide plus radiotherapy; GTR, gross total resection; NA, not applicable; RT, radiotherapy alone; STR, subtotal resection.

[a]Chi-square test.

[b]Mann-Whitney *U* test.

[c]Fisher exact test.

were 56.6% (95% CI, 42.9–74.5) in the CRT group and 33.3% (95% CI, 17.3–64.1) in the RT-alone group. The median OS (25.8 months vs 17.2 months; HR, 0.362; 95% CI, 0.192–0.681; $p = .001$) and PFS (14.2 months vs 7.1 months; HR, 0.387; 95% CI, 0.187–0.798; $p = .002$) were significantly longer in CRT group than that in RT-alone group (Figure 2).

Univariate analysis revealed that KPS >70 (HR, 0.472; $p = .033$) and chemotherapy (HR, 0.346; $p = .002$) were protective factors for PFS. Chemotherapy (HR, 0.362; $p = .002$) significantly affected OS (Table 3). In the multivariate analysis, the clinical benefit of TMZ on OS (CRT vs. RT only, HR, 0.314; 95% CI, 0.163–0.604; $p = .001$) and PFS (HR, 0.383; 95% CI, 0.206–0.711; $p = .002$; Table 3) was still apparent in this cohort of patients. In addition, single-lobe invasion (HR, 0.424; 95% CI, 0.219–0.822; $p = .011$) and lower histological grade (HR, 0.472; 95% CI, 0.245–0.907; $p = .024$) were favorable prognostic variables for OS (Table 3). In the entire CRT group, MGMT promoter methylation showed no prognostic influence (Figure 3).

In sensitivity analyses addressing potential confounding through propensity score adjustment, the treatment effects remained consistent with the primary findings for both PFS and OS. For PFS, HR for CRT versus RT was 0.393 (95% CI, 0.174–0.889; $p = .025$) using

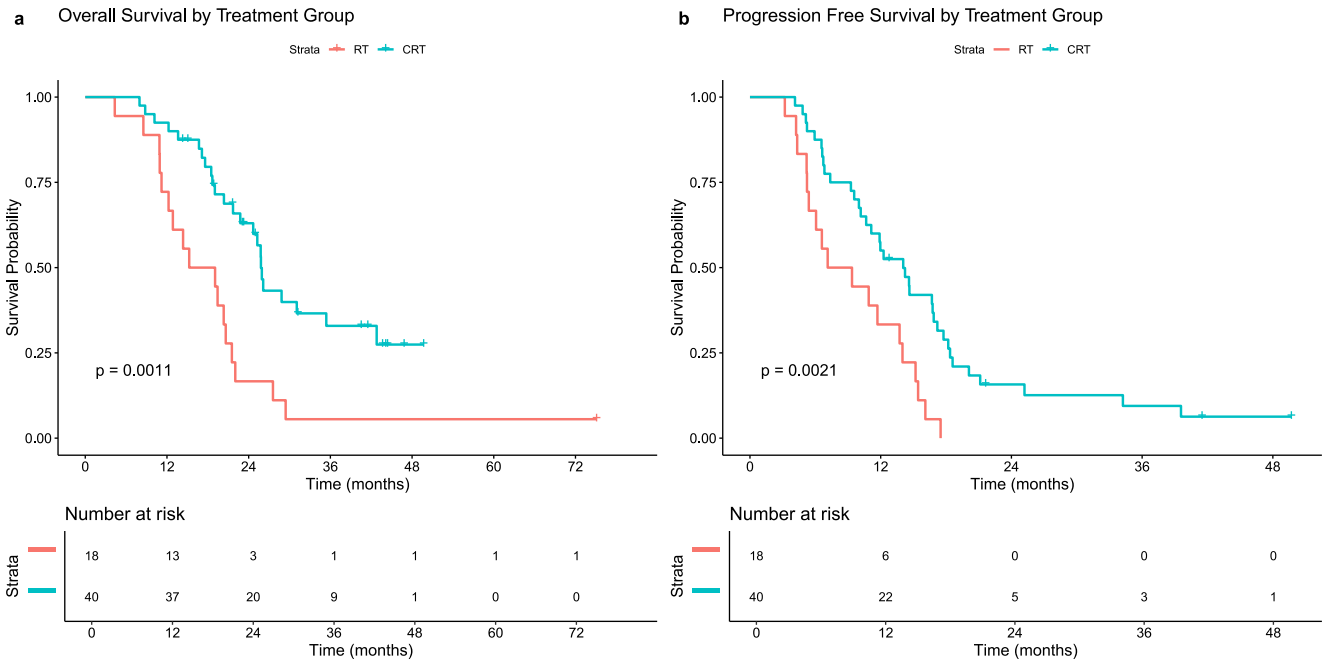

FIGURE 2 Kaplan–Meier curves of patients enrolled in RT and CRT group showing significantly longer median overall survival (OS) and progression-free survival (PFS) in the CRT group than in the RT group. Strata means stratification. (A) OS; (B) PFS. CRT indicates temozolomide plus radiotherapy; RT, radiotherapy alone.

TABLE 3 Univariate analysis and multivariate analysis for PFS and OS based on clinical and molecular variables.

	Univariate analysis						Multivariate analysis					
	PFS			OS			PFS			OS		
Variables	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI
Sex (male vs. female)	0.682	1.154	0.582–2.286	0.506	1.247	0.650–2.391	0.378	0.754	0.402–1.414	0.318	1.428	0.709–2.873
Age (continuous, per year increase)	0.779	1.146	0.444–2.960	0.875	1.078	0.422–2.755	0.522	1.350	0.539–3.380	0.775	1.159	0.422–3.185
Single lobe (yes vs. no)	0.160	0.615	0.312–1.212	0.063	0.547	0.290–1.032	0.406	0.776	0.428–1.410	0.011	0.424	0.219–0.822
GTR (yes vs. no)	0.217	0.573	0.237–1.387	0.116	0.520	0.229–1.176	0.095	0.472	0.196–1.141	0.077	0.464	0.198–1.087
KPS (>70 vs. ≤70)	0.033	0.472	0.237–0.943	0.012	1.505	1.092–2.075	0.523	0.801	0.405–1.584	0.147	1.302	0.911–1.859
Histology grading (grade 2 vs. 3)	0.060	0.510	0.253–1.029	0.063	0.543	0.285–1.033	0.194	0.679	0.378–1.218	0.024	0.472	0.245–0.907
MGMTp-meth (yes vs. no)	0.162	1.596	0.829–3.073	0.121	1.625	0.880–3.001	0.063	0.551	0.294–1.032	0.151	1.609	0.841–3.076
Chemotherapy (yes vs. no)	0.002	0.346	0.177–0.675	0.002	0.362	0.192–0.681	0.002	0.383	0.206–0.711	0.001	0.314	0.163–0.604

Abbreviations: GTR, gross tumor resection; KPS, Karnofsky performance scale; NA, not applicable; OS, overall survival; PFS, progression-free survival.

propensity score matching and 0.375 (95% CI, 0.217–0.647; $p < .001$) with inverse probability of treatment weighting. Similarly for OS, adjusted analyses showed HRs of 0.368 (95% CI, 0.171–0.791; $p = .01$) with matching and 0.436 (95% CI, 0.214–0.957; $p = .006$) with weighting. The stability of these effect estimates across different analytical approaches supports the robustness of the observed clinical benefit favoring CRT in both survival endpoints (Supplementary Table 1). Covariate balance before and after adjustment is detailed in Supplementary Figure 1.

Disease progression and toxic effect

Ninety-five percent of the 41 patients died because of disease progression. One patient died of therapy-unrelated cerebral hemorrhage without tumor recurrence and one died of therapy-related pneumonia in the RT group. Local, distant, and multifocal tumor recurrences were observed in 14 (35.0%), 13 (32.5%), and seven patients (17.5%) in the CRT group and in nine (50.0%), five (27.8%), and four patients (22.2%) in the RT group, respectively. There were three patients in the CRT

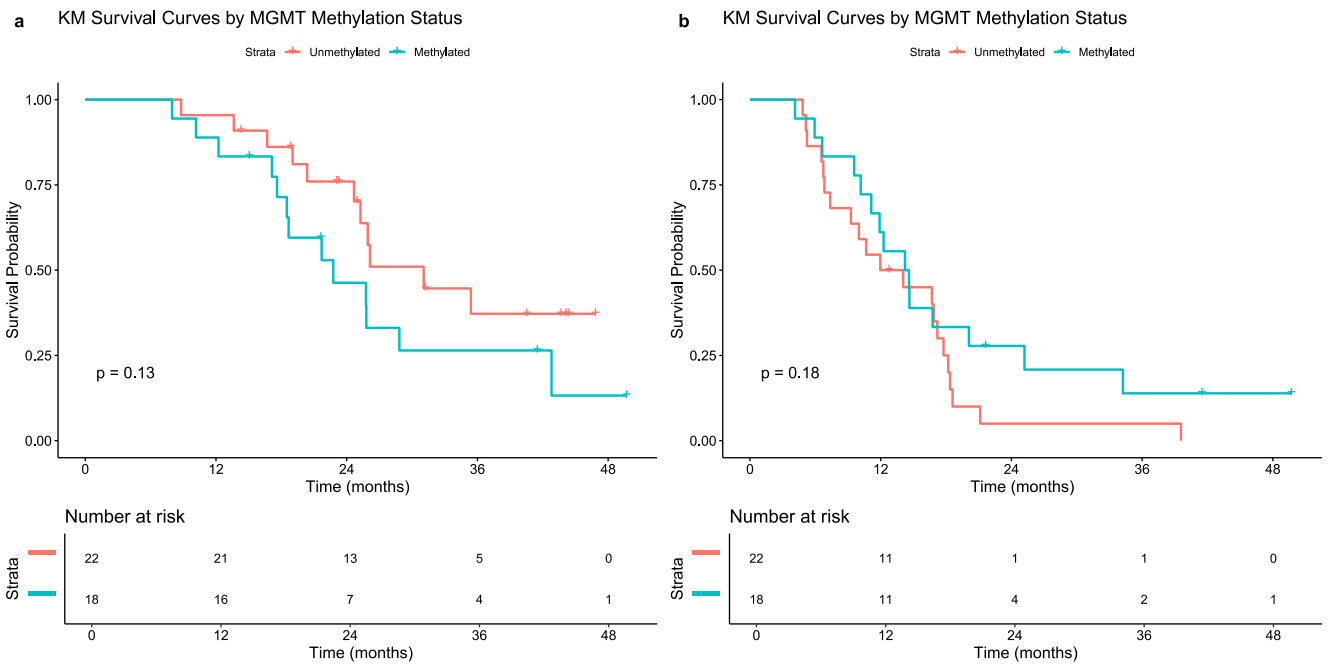

FIGURE 3 Kaplan–Meier curves of comparison between patients with different MGMT promoter methylation status showing no significant difference in overall survival (OS) and progression-free survival (PFS) between patients with different MGMT promoter methylation status among the 40 patients in the CRT group. Strata means stratification. (A) OS; (B) PFS. CRT indicates temozolomide plus radiotherapy. MGMT, O6-methylguanine-DNA methyl-transferase.

group and one patient in the RT group with spinal recurrence. Among the 17 patients with tumor progression in the RT group, eight (47.1%) underwent salvage treatment, including TMZ and bevacizumab. The remaining nine patients (52.9%) did not receive any salvage therapy. Among the 34 patients with tumor progression in the CRT group, 16 (47.1%) underwent salvage chemotherapy and four (11.8%) received salvage surgery followed by chemotherapy.

Overall, the treatments were well-tolerated (Supplementary Table 2). In the CRT group, 18 patients exhibited various grade 1 toxicity symptoms and five exhibited grade 2 toxicity symptoms. In the RT group, six patients experienced grade 1 toxicity, one experienced grade 2 toxicity, and one experienced grade 3 toxicity.

DISCUSSION

This study aimed to determine whether the addition of TMZ to RT prolonged survival among patients with histological grade 2/3 $G_{IDH\text{-}wt/TERTp\text{-}mut}$, meeting the WHO 2021 molecular criteria for glioblastoma, IDH-wt. In the present study, we observed the median OS and PFS were significantly longer in the CRT group than in the RT alone group with manageable toxicity.

The median age of patients in this study was similar to that of patients with primary glioblastoma in the CGGA database (median age, 51 years) and historical cohorts (median age, 56 years).[14,15] However, the OS was slightly longer than that reported in the CGGA database (24.7 vs. 14.9 months) and historical data (24.7 vs. 14–16 months).[14,15] Similar to primary glioblastoma, patients with histological grade 2/3 $G_{IDH\text{-}wt/TERTp\text{-}mut}$ can benefit from combined chemotherapy and radiotherapy compared to radiotherapy alone. However, although MGMT promoter methylation serves as a prognostic marker and predictor of sensitivity to alkylating chemotherapy in histologically defined glioblastoma,[16] its significance was not observed in molecularly defined glioblastoma. Our findings indicate that patients with MGMT promoter methylation did not derive additional benefits from TMZ chemotherapy. To further explore the biological significance and clinical implications of MGMT promoter status in IDH-wt/TERTp-mutant gliomas, Teske et al. described the pattern and extent of MGMT promoter methylation in 57 IDH-wt astrocytoma patients with TERTp-mut and 224 glioblastoma patients defined by histopathology.[17] Their study revealed that the extent of MGMT promoter methylation was comparable between the two groups. In patients with molecularly defined glioblastoma treated with alkylating chemotherapy, MGMT promoter methylation was associated with improved PFS, although statistical significance for OS was not achieved. Notably, a trend toward better outcomes was observed in tumors with more than 18 methylated CpG sites. It is crucial to emphasize that MGMT promoter methylation status alone is not the sole determinant of TMZ response. Post-translational modifications and cellular repair mechanisms may affect the response of tumor cells to treatment.

Recently, a meta-analysis that includes the RTOG 9802, RTOG 9402, EORTC 26951, and CATNON trials was performed to determine the effect of alkylating chemotherapy on IDH-wt gliomas.[18] The meta-analysis showed addition of alkylating chemotherapy to radiotherapy was not associated with a significantly reduced risk of death ($p = 0.17$) in patients with IDH-wt glioma.[18] Similarly, the addition of alkylating chemotherapy to radiotherapy was also not associated with improved OS or PFS for patients with IDH-wt tumors meeting

the WHO 2021 molecular criteria for GBM ($p = 0.25$).[18] We compared the characteristics and treatment methods of different clinical trials[19–23](Supplementary Table 3). The primary distinction between this study and previous clinical trials is our exclusive enrollment of patients with IDH wild-type and TERT promoter mutations, resulting in a homogeneous patient cohort that enhances the reliability of our data.

First, with the update of the classification of central nervous system tumors, the diagnostic criteria for glioma grading have also changed significantly. For example, the 2016 classification introduced the pivotal integration of molecular parameters with histology,[10] and the 2021 classification further clarified that TERT promoter mutation in IDH-wt diffuse astrocytic tumors is sufficient for a diagnosis of glioblastoma, WHO grade 4, even in the absence of classic high-grade histological features.[1] This evolution means that a tumor that might have been diagnosed as a lower grade glioma a decade ago based on histology alone is now molecularly classified as glioblastoma. These studies, spanning decades, are heterogeneous in diagnosis. Some gliomas originally diagnosed as grade 3 are now classified as WHO grade 4. Notably, the IDH-wt subgroup in the CATNON trial accounted for one third of the total, which is higher than the actual proportion.[24] Therefore, discrepancies between our data and international reports on the proportion of IDH-wt gliomas may also have influenced the results.[25] In addition, IDH-wt gliomas with isolated TERT promoter mutations have better survival than other mGBM.[26] Second, variations in treatment approaches may contribute to differences in trial outcomes. For instance, the radiotherapy doses differed significantly: histological grade 2 gliomas typically received a total dose of 54 Gy (RTOG 9802 and RTOG 0424), whereas grade 3 gliomas were treated with 59.4 Gy in 33 fractions (RTOG 9402, EORTC 26951, and CATNON). In contrast, all patients in our study received a uniform dose of 60 Gy in 30 fractions. Previous studies have demonstrated that in low-grade diffuse astrocytomas, OS and PFS are significantly correlated with radiotherapy dose. Specifically, high-dose RT (≥54 Gy) was associated with improved 5-year OS and PFS.[7] It is possible that inconsistencies in outcomes from prior clinical trials involving IDH-wt and TERT promoter-mutant gliomas may be attributed to these variations in radiotherapy dosing.

Retrospective studies have identified many prognostic factors, including the extent of resection, histology, tumor size, performance status, and tumors crossing the midline for low-grade gliomas.[27,28] The prognostic significance of the extent of resection in mGBM remains controversial.[29] Ruda et al. and Ramos-Fresnedo et al. identified no survival benefit from GTR of mGBM.[30,31] A recent retrospective study showed that the GTR of contrast-enhancing and nonenhancing tumors was independently associated with better survival in IDH-wt glioblastomas, including a portion of histological grade 2/3 IDH-wt gliomas with the molecular features of glioblastomas.[32] In our study, the Cox model identified GTR as a favorable prognostic variable for PFS but not for OS. In addition, a lower histological grade was an independent prognostic factor for OS, which is consistent with the results reported by Berzero et al. A retrospective study reported a median survival of 42 months in patients with mGBMs that were histological grade 2 tumors, which was substantially longer than that of patients with mGBMs that were histological grade 3 gliomas (median OS, 17 months).[26] A meta-analysis of mGBM prevalence and OS according to the PRISMA statement showed that patients with histological grade 3 gliomas had worse OS than those with grade 2 tumors in the pooled results, which was consistent with these findings.[33]

Our study has several limitations that should be considered when interpreting the findings. First, the overall sample size, particularly in the RT group, was relatively small. This limited number of events may have introduced an imbalance in patient characteristics and influenced the observed rates of salvage therapy, making the comparison susceptible to chance findings. Second, the decision to pursue salvage therapy is complex and can be influenced by additional unmeasured confounding factors, such as socioeconomic status and patient preferences, which were not fully captured in our analysis. We hypothesize that the significantly longer PFS in the CRT group fostered higher expectations and a greater willingness to pursue salvage therapy, whereas the shorter PFS in the RT group led to diminished expectations, influencing the decision to opt for supportive care. Therefore, the differences in salvage rates between groups should be interpreted with caution, and our hypotheses regarding patient expectations warrant validation in larger, prospective cohorts. This study is an encouraging prerequisite for validating these findings in a large multicenter prospective randomized trial.

CONCLUSION

Patients with newly diagnosed IDH-wt/TERTp-mut grade 2/3 gliomas treated with RT combined with concurrent and adjuvant TMZ have significantly better OS and PFS than those treated with RT alone. The addition of TMZ did not significantly increase the incidence of adverse reactions.

AUTHOR CONTRIBUTIONS

Jing Zhang: Conceptualization; methodology; writing—original draft; writing—review and editing; formal analysis; data curation; investigation. **Peng Wang**: Conceptualization; investigation; writing—original draft; writing—review and editing; methodology; validation; visualization; software; formal analysis; data curation. **Yin Ren**: Writing—review and editing; methodology; validation; formal analysis. **Li Chen**: writing—review and editing; investigation; validation; data curation; resources. **Jin Feng**: Resources; data curation; validation; investigation; writing—review and editing. **Fei Liu**: Writing—review and editing; methodology; data curation. **Kaiwen Deng**: Writing—review and editing; software; visualization. **Zhaoshi Bao**: Writing—review and editing; methodology; resources; supervision; data curation; project administration; validation; investigation. **Xiaoguang Qiu**: Conceptualization; writing—review and editing; supervision; resources; validation; funding acquisition; project administration. **Yanwei Liu**: Resources; project administration; writing—review and editing; writing—original draft; funding acquisition; supervision; methodology; validation; conceptualization; investigation.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data will be made available upon reasonable request. The corresponding author of this article can be contacted by email for original data.

PATIENT CONSENT STATEMENT

Informed consent was obtained from all individual participants included in the study.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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