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Original Article

Chemoradiotherapy with temozolomide vs. radiotherapy alone in patients with *IDH* wild-type and *TERT* promoter mutation WHO grade II/III gliomas: A prospective randomized study ☆

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ABSTRACT

Purpose: Patients with grade II/III diffuse glioma (lower grade glioma, LGG) with isocitrate dehydrogenase wild-type (*IDH*-wt) and telomerase reverse-transcriptase promoter mutation (*TERT*p-mut) experience shorter overall survival (OS) time than *IDH* mutant patients. The optimal treatment strategy for these patients is unclear. We compared the effects of radiotherapy (RT) alone vs. RT concurrent with temozolomide (TMZ) followed by adjuvant TMZ in these LGG patients.

Patients and methods: Thirty-seven LGG patients with *IDH*-wt and *TERT*p-mut were randomly allocated to either RT alone treatment (RT group, n = 18; 60 Gy in 30 daily fractions) or RT concurrent with TMZ (75 mg/m^2/d, 7 d/week) followed by adjuvant TMZ (CRT group, n = 19). The median follow-up duration was 17 months. Log-rank test was used for OS and PFS comparisons.

Results: The 1-year OS rate was 94.1% [95% confidence interval (CI) 82.9–100] in the CRT group and 74.6% (95% CI, 52.9–96.4) in the RT group. The median OS values in the CRT and RT groups were statistically different [25 vs. 17 months, respectively; hazard ratio (HR) 0.271; 95% CI, 0.092–0.793; P = 0.017], while PFS values were not (16 vs. 7 months, respectively; HR, 0.917; 95% CI, 0.397–2.120; P = 0.840). Multivariate analysis indicated that CRT treatment and female sex were associated with significantly longer OS (P = 0.001, P = 0.016, respectively).

Conclusion: CRT treatment for *IDH*-wt/*TERT*p-mut grade II/III gliomas resulted in significantly longer OS than RT alone. Female sex was a significant favorable prognostic factor.

The World Health Organization (WHO) grades II and III diffuse gliomas (sometimes described as lower grade gliomas, LGG) as infiltrative neoplasms arising from glial cells (astrocytes and oligodendrocytes) in the central nervous system (CNS). Considering the limitations of conducting LGG clinical trials, such as tumor rarity and relatively long follow-up, the treatment strategies remain unclear. Currently, the treatment mainly involves surgical resection followed by radiotherapy (RT) [1–3].

The clinical behavior features of WHO grade II/III gliomas cannot be precisely predicted based on histological classification, which necessitates the use of genetic classification to guide clinical strategy [3–5]. Molecular features used for classification include mutations in specific genes (e.g., isocitrate dehydrogenase gene, *IDH* [6,7]), chromosomal loss or other large-scale deletions (e.g., co-deletion of chromosome arms 1p/19q [8]), and gene promoter methylation status [e.g., *MGMT* promoter (*MGMT*p) methylation [9]].

Majority of WHO grade II/III gliomas in adults (70–80%) harbor mutations in the isocitrate dehydrogenase (*IDH*) 1 and 2 genes, which define a subtype associated with a favorable prognosis [6,7]. Patients with such tumors have a better outcome than those with wild-type *IDH* (*IDH*-wt) genes. However, the lack of *IDH* mutation in LGG does not uniformly represent aggressive behavior as glioblastoma (GBM) [10]. Therefore, additional markers, such as mutations in the telomerase reverse transcriptase (*TERT*) gene promoter (*TERT*p-mut) [11,12], are used to stratify WHO grade II/III gliomas into prognostic subgroups in combination with *IDH* mutation status [13]. Indeed, the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) recommends that grade II or III IDH-wt diffuse astrocytic gliomas

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that possess either *EGFR* amplification, combined whole chromosome 7 gain and chromosome 10 loss, or *TERT*p-mut should be classified as "diffuse astrocytic glioma, *IDH*-wt, with molecular features of GBM, WHO grade IV" [14].

We have previously shown [15] that patients with *IDH*-wt and *TERT*p-mut (28/377, 7.4%) have worse clinical outcomes [median overall survival time (OS), 27.7 months] than patients with different mutation status. This was also reported by others [13,16–18]. However, current treatment strategies are not tailored for this subtype of gliomas because of dearth of clinical data.

RT with concomitant and adjuvant temozolomide (TMZ) treatments (Stupp schedule) has emerged as a standard of care for patients with good performance status non-elderly GBM [19]. The benefits of TMZ as adjuvant therapy for WHO grade II/III gliomas were also reported [2]. However, no studies are available on the benefit of concurrent and adjuvant TMZ therapy in patients with *IDH*-wt/*TERT*p-mut subgroup of WHO grade II/III gliomas. Considering the dismal prognosis of these patients, concurrent TMZ therapy followed by adjuvant TMZ therapy, as a relatively more aggressive strategy than RT alone, should be evaluated.

Accordingly, in the present prospective randomized study, we examined the efficacy and safety of RT concurrent with TMZ followed by adjuvant TMZ (CRT treatment) in patients with WHO grade II/III glioma with *IDH*-wt and *TERT*p-mut.

Patients and methods

Patient eligibility

Patients with histologically confirmed supratentorial infiltrating WHO grade II/III diffuse gliomas, including anaplastic astrocytoma (AA) with *IDH*-mut/wt and diffuse astrocytoma (A) with *IDH*-mut/wt, were screened. The mutation status of *IDH1*, *IDH2*, and *TERT*p, and *MGMT*p methylation status (associated with response to treatment in malignant glioma [20]) were determined by pyrosequencing or Sanger sequencing (see below); 1p/19q loss of heterozygosity, associated with the oligodendroglial histologic type and with sensitivity to chemotherapy with alkylating agents [18], was determined by fluorescence *in situ* hybridization (see below). Only patients with *IDH*-wt/*TERT*p-mut and 1p/19q non–co-deletion cases were enrolled. Written informed consent was obtained from all patients before enrollment. Additional eligibility requirements were as follows: (i) over 18 and under 70-years-old; (ii) the Karnofsky performance status (KPS) score $\geq$60; (iii) adequate bone marrow (neutrophilic granulocyte count >1500/μl; platelet count >100,000/μl; haemoglobin >10 g/dl), renal (serum creatinine <1.7 mg/dL), and hepatic (serum total bilirubin $\leq$2.0 mg/dL, AST or ALT <1.5 times the upper normal limit) functions; (iv) life expectancy over 8 weeks; (v) no previous systemic chemotherapy; (vi) no previous RT to the brain. Patients with serious medical or neurological condition were excluded. Also excluded were patients with contraindications to RT or TMZ chemotherapy; those unable to follow the procedures, visits, and examinations described in the study protocol; those with a second cancer requiring RT or chemotherapy; those unable to undergo gadolinium-contrasted magnetic resonance imaging (MRI); and those who were pregnant or nursing. The ethics committee of Beijing Tiantan Hospital approved the protocol and informed consent document (number KY2016-032-03).

Study design

This prospective randomized study consisted of two steps, an initial registration step at any time after the initial diagnosis, allowing for molecular analyses required for stratification; and a randomization step at the time point when treatment was clinically indicated. All patients had undergone surgical resection or biopsy. Within 6 weeks after histological diagnosis of WHO grade II/III gliomas, the eligible patients were randomly assigned to one of the two treatment arms using a computer-generated randomization schedule. Control group patients underwent intensity-modulated RT (IMRT) or 3-dimensional conformal RT 5 d/week for 6 weeks (for a total of 60 Gy). RT was planned with gadolinium-enhanced MRI performed within 2 weeks of randomization. The initial field was the T2-weighted abnormality plus a 2-cm margin (46 Gy in 23 fractions). The boost field was the enhanced T1-weighted abnormality plus a 1-cm margin (14 Gy in 7 fractions). The experimental group patients underwent IMRT or 3-dimensional conformal radiation therapy 5 d/week for 6 weeks (for a total of 60 Gy) and received TMZ (75 mg/m^2/d, 7 d/week) for up to 7 weeks. Four weeks after the completion of chemotherapy and RT, the patients received TMZ on days 1–5 (150–200 mg/m^2). TMZ treatment was repeated every 28 d for up to 12 courses. The assigned treatment began within 1 week after randomization. No standard salvage treatment was designed because of insufficient clinical evidence. In practice, salvage surgery was the first choice of treatment after progression. Other treatments included chemotherapy with TMZ or intravenous chemotherapy. In order to prevent severe radiation injury, few patients had the opportunity to undergo salvage RT. Toxicities were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, version 4.0).

Evaluations

Baseline examinations included physical examination, brain MRI, full blood cell counts, and blood chemistry, including renal and hepatic function, chest X-ray, and color Doppler echocardiography. Pre- and postoperative MRI scans, including T1 images with and without contrast, as well as T2 and fluid-attenuated inversion recovery images, were acquired. The maximum preoperative tumor diameter, based on the axial and/or coronal T2 or fluid-attenuated inversion recovery images, was measured and recorded at the time of study entry, as was the presence or absence of contrast enhancement, based on the T1 images with contrast. The extent of surgical resection was determined based on the neurosurgeon's assessment, as recorded in the operative report, and also on the comparison of pre- and postoperative MRI data, to quantify the amount of residual tumor. Patients were seen weekly during RT and received a full clinical examination, blood hematology, and chemistry test screen prior to every cycle of chemotherapy. Tumor response and progression were defined according to the Response Assessment in Neuro-Oncology (RANO) criteria [21]. After RT treatment, all patients (37/37, 100%) underwent brain MRI in weeks 2–6, followed by clinical and radiographic monitoring every 3–4 months. Tumor progression was confirmed in patients whose clinical condition deteriorated, with MRI-determined tumor recurrence (27/27, 100%). After progression, 10 (10/27, 37%) patients ceased to undergo MRI scanning because of poor physical condition.

Molecular assessments

The mutation status of *IDH1* and *IDH2*, and *MGMT*p methylation status were determined using DNA pyrosequencing, as described previously [8]. The mutation status of *TERT* promoter was determined by Sanger sequencing [15]; 1p/19q co-deletion testing was performed using fluorescence *in situ* hybridization [22].

Statistical methods

The primary endpoint for the analysis of treatment efficacy was OS, and the secondary endpoint was PFS. OS was defined as the

time from randomization to the date of death from any cause, or last follow-up. PFS was defined as the time from randomization to the date of initial disease progression, disease recurrence, or last follow-up. The calculated sample size of the study was 60 for a power of 80% and a significance level of 5% (two-sided) for detecting a 30% increase in 1-year OS rate, i.e., from 70% in the control group to 91% in the experimental group. However, because of the difficulty of enrolling a sufficient number of patients representing the rare LGG subgroup analyzed in this single-center study, the sample size was 18 (for the control, RT, group) and 19 (for the experimental, CRT, group). PFS and OS were estimated by using the Kaplan–Meier method. Survival in the groups was compared using the log-rank test. The distribution of categorical variables in the two groups was tested using the χ^2 test, and the distribution of continuous variables was assessed using the *t*-test. Multivariate Cox proportional-hazards analysis was used to investigate the relative importance of different prognostic factors for OS. All analyses were performed using SPSS statistical analysis software v20 and *P*-values below 0.05 were considered statistically significant.

Data availability statement

For qualified investigators, anonymized data from our hospital can be made available on request to the corresponding authors.

Results

Between September 2016 and December 2019, 37 eligible patients were enrolled in the study at Beijing Tiantan Hospital. The date of last follow-up was April 24, 2020. The median follow-up duration was 17 months. The median age was 52 years (range, 19–67 years). The median KPS score at randomization was 80 (range, 60–100). Surgery was the primary treatment, and was classified as gross total resection (n = 19), subtotal resection (n = 12), partial resection (n = 4), and biopsy only (n = 2). Central pathology review confirmed the presence of AA with *IDH*-mut/wt in 21 patients, and A with *IDH*-mut/wt in 16 patients. Molecular assessment confirmed that all enrolled patients were *IDH*-wt, 1p/19q non–co-deletion, and *TERT*p-mut. *MGMT*p methylation analysis was also performed. The enrolled patients were randomly assigned to receive either RT alone (n = 18) or RT concurrent with TMZ followed by adjuvant TMZ (CRT) therapy (n = 19). The characteristics of the two treatment groups were well balanced at baseline (Table 1), with no significant differences in KPS, sex, age, extent of resection, tumor location, pathologic classification, and *MGMT*p methylation status. RT was planned with gadolinium-enhanced MRI, administered within 2 weeks of randomization. All patients underwent IMRT (a total dose of 60 Gy), none of patients received RT using 3D-CRT technique. After completion of RT concurrent with TMZ, the CRT group patients received up to 12 cycles of adjuvant TMZ (median, 12; range, 2–12). Treatment-related toxicity did not lead to permanent cessation of chemotherapy. Tumor progression-caused chemotherapy cessation was observed in 3 patients (15.8%).

Of 37 patients, 15 (40.5%) had died by the time of the last follow-up. In the RT group, 9 patients died of disease progression, and one died of therapy-unrelated cerebral hemorrhage without tumor recurrence. Five patients in the CRT group died of tumor progression. The 1-year OS rate was 94.1% [95% confidence interval (CI) 77.8–100] in the CRT group and 74.6% (95% CI 42.7–94.1) in the RT group. The median OS values in the CRT group and RT group were statistically different [25 vs. 17 months, respectively; hazard ratio (HR) 0.271; 95% CI, 0.092–0.793, P = 0.017] (Fig. 1). Four of ten CRT group patients with methylated *MGMT*p died, while 1 of 9 patients with unmethylated *MGMT*p died.

Table 1
Patient characteristics.

Patient Characteristics	RT Group (n = 18)	CRT Group (n = 19)	*P*-value
Sex			
Male	12 (66.7%)	14 (73.7%)	
Female	6 (33.3%)	5 (26.3%)	0.641*
Age (Median)	52	48	0.366
Extent of resection			
GTR	12 (66.7%)	7 (36.8%)	
STR	3 (16.7%)	9 (47.4)	
PR	2 (11.1%)	2 (10.5%)	
Bx	1 (5.6%)	1 (5.3%)	0.335*
Pathologic classification			
A	7 (38.9%)	9 (47.4%)	
AA	11 (61.1%)	10 (52.6%)	0.603*
MGMTp-meth			
Yes	6 (33.3%)	10 (52.6%)	
No	12 (66.7%)	9 (47.4%)	0.236*
Multifocal tumor			
Yes	9 (50%)	9 (47.4%)	
No	9 (50%)	10 (52.6%)	0.873*
KPS score			
≤70	9 (50%)	5 (26.3%)	
>70	9 (50%)	14 (73.7%)	0.171*

Abbreviations: A, diffuse astrocytoma; AA, anaplastic astrocytoma; Bx, biopsy; CRT, chemoradiotherapy; GTR, gross total resection; KPS, Karnofsky performance status; MGMTp-meth, methylation of *O*-6-methylguanine-DNA methyltransferase gene promoter; PR, partial resection; RT, radiotherapy; STR, subtotal resection.
*P values are based on the χ^2 test.

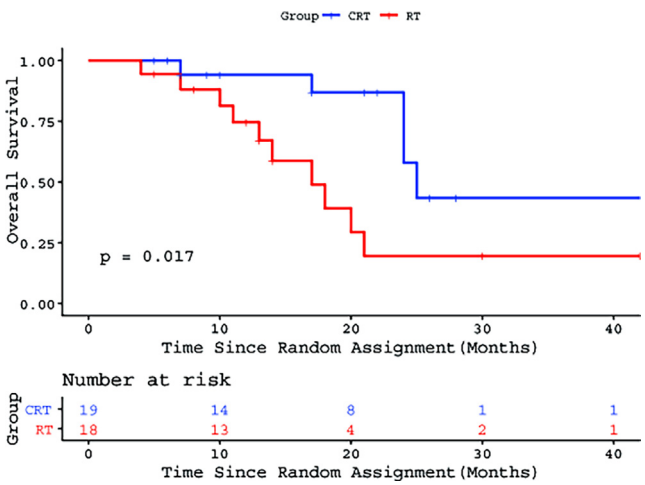

Fig. 1. Kaplan-Meier estimates of the overall survival, by treatment, of patients with IDHwt/TERTp-mut grade II/III gliomas (RT, RT alone group; CRT, Chemoradiotherapy group). (The *P*-value was determined by log-rank test).

No significant difference in PFS between the CRT group and RT group was noted (16 vs. 7 months, respectively; HR, 0.917; 95% CI, 0.397–2.120; P = 0.840) (Fig. 2). Local, distant, and multifocal tumor recurrence patterns were observed in 6 (31.6%), 2 (10.5%), and 6 patients (31.6%) in the CRT group, respectively; and in 4 (22.2%), 3 (16.7%), and 4 patients (22.2%) in the RT group, respectively. No significant difference in local and multifocal recurrence between the two treatment groups was noted. Among 11 patients with tumor progression in the RT group, only 4 underwent salvage chemotherapy and all died after treatment; 6 of 7 patients who did not receive any salvage treatment died of tumor progression. Among 14 patients with tumor progression in the CRT group, 7 (50%) underwent salvage chemotherapy and 2 (14.3%) received salvage surgery followed by chemotherapy. Three patients who

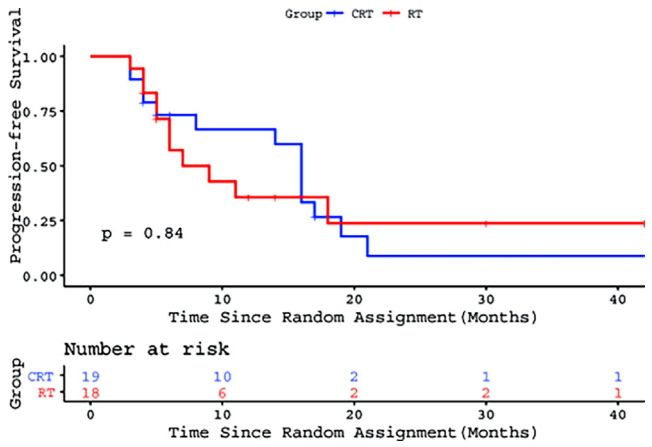

Fig. 2. Kaplan-Meier estimates of progression-free survival, by treatment, of patients with IDHwt/TERTp-mut grade II/III gliomas. (RT, RT alone group; CRT, Chemoradiotherapy group). (The *P*-value was determined by log-rank test).

received salvage chemotherapy died and others remain alive. Two of five patients who did not receive salvage treatment died of tumor progression.

Overall, the treatments were well tolerated (Table 2). In the CRT group, 7 patients exhibited various grade 1 toxicity symptoms and 2 exhibited grade 2 toxicity symptoms. In the RT group, 2 patients experienced grade 1 toxicity; 1 experienced grade 2 toxicity; and 1 experienced grade 3 toxicity.

Clinical features and therapy were evaluated as OS prognostic factors by univariate analysis (Table 3). The treatment and sex were statistically significant for the clinical outcome. Age, extent of resection, KPS score, pathologic classification, *MGMT*p methylation status, and tumor location did not influence OS. Next, multivariate Cox proportional-hazards model for OS was calculated. It included treatment (CRT vs. RT alone), sex (male vs. female), pathologic classification (A vs. AA) and GTR (yes vs. no) comparisons (all with $P < 0.1$ in the univariate analysis) (Table 4). After adjusting for these factors, the OS HR for CRT vs. RT alone was 0.047 (95% CI, 0.008–0.290; $P = 0.001$), and for female vs. male was 0.132 (95% CI, 0.025–0.687; $P = 0.016$). The sex and extent of resection influenced PFS in the univariate analysis, yet were not statistically significant in the Cox model.

Discussion

Because of the scarcity of clinical data, the treatment strategy for WHO grade II/III gliomas classified on the basis of *IDH* and *TERT*p mutation status is not established. We thus investigated the effectiveness of CRT vs. RT treatment in the *IDH*-wt/*TERT*p-mut patient subset. We showed that the 1-year OS rate was 94.1% in the CRT group and 74.6% in the RT alone group ($P = 0.017$). Further, multivariate analysis revealed that the OS HR for CRT vs. RT was 0.047 (95% CI, 0.008–0.290; $P = 0.001$). These observations support significant and clinically meaningful benefits for OS of RT concurrent with TMZ followed by adjuvant TMZ in these patients, providing preliminary evidence in support of offering this treatment.

Standard treatment, involving surgery with adjuvant RT, is not adequate for treating *IDH*-wt/*TERT*p-mut grade II/III glioma patients [15]. Since concurrent CRT with TMZ is the standard of care for GBM, treatment of *IDH*-wt/*TERT*p-mut grade II/III glioma patients with Stupp schedule has been suggested [9]. Zhang et al. [20] combined *TERT*p and *IDH* mutations to stratify WHO grade II and III diffuse gliomas into four subgroups, and predicted differential responses to adjuvant therapies. Univariate analysis revealed that RT and CRT were significant factors impacting the PFS in the *IDH*-wt/*TERT*p-mut subgroup ($n = 20/295$, 6.8%) (RT, $P = 0.015$; CRT, $P = 0.015$). However, comparison of RT vs CRT was not performed in this study. Here, we compared the clinical effect of both treatment strategies and have confirmed the benefits of the Stupp schedule for this molecular type of GBM. Recently, the 2021 WHO Classification of Tumors of the Central Nervous System grouped the IDH-wt/TERTp-mut grade II/III gliomas to "GBM, IDH-

Table 3
Univariate analysis of patient characteristics.

Variable	Case	MST (mo)	95% CI	*P*-value
Age				
≤40	9	24.0	19.5–28.5	
>40	28	24.0	14.0–34.0	0.627
KPS score				
≤70	14	20.0	13.0–27.0	
>70	23	24.0	20.0–28.0	0.193
MGMTp-meth				
Yes	16	24	11.8–36.2	
No	21	24	18.0–30.0	0.268
CRT				
Yes	19	25.0	22.5–27.4	
No	18	17.0	11.3–22.7	0.017
GTR				
Yes	19	24	N/A	
No	18	20	11.4–28.6	0.102
Pathologic classification				
A	16	N/R		
AA	21	21	16.8–25.2	0.068
Multifocal tumor				
Yes	18	20.0	10.6–29.4	
No	19	25.0	19.9–30.1	0.213
Sex				
Male	26	18	12.4–23.6	
Female	11	N/R		0.042

Abbreviations: A, diffuse astrocytoma; AA, anaplastic astrocytoma; CRT, chemoradiotherapy; CI, confidence interval; GTR, gross total resection; KPS, Karnofsky performance scale; MGMTp-meth, methylation of *O*-6-methylguanine-DNA methyltransferase gene promoter; MST, median survival time; N/A, not available; N/R, not reached.

Table 2
Treatment toxicities.

Event	RT group ($n = 18$)			CRT group ($n = 19$)		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Hemtologic toxicity	0	0	0	2	1	0
Vomiting	0	0	0	2	0	0
Amnesia	2	1	0	3	0	0
Encephalopathy	0	0	1	0	0	0
Cerebral necrosis	0	0	0	0	1	0

Abbreviations: CRT, chemoradiotherapy; RT, radiotherapy.

Table 4
Multivariate analysis of patient characteristics.

Variable	Hazard Ratio	95% CI	*P*-value
Sex			
Male	1		
Female	0.132	0.025–0.687	0.016
CRT			
Yes	0.047	0.008–0.290	
No	1		0.001
GTR			
Yes	1		
No	4.522	1.264–16.181	0.020
Pathologic classification			
A	1		
AA	2.068	0.671–6.367	0.206

Abbreviations: A, diffuse astrocytoma; AA, anaplastic astrocytoma; CRT, chemoradiotherapy; GTR, gross total resection.

wildtype" [23]. Our findings support this modified classification and indicate that concurrent CRT and adjuvant TMZ could be the standard treatment protocol for this subtype.

The *IDH*-wt/*TERT*p-mut subgroup accounts for approximately 7–10% of grade II/III gliomas [15,20,24], which is a major factor limiting the sample size and statistical power for analyzing the effects of any therapeutic strategies tested in this group. Nonetheless, in this single-center study, we managed to collate the largest cohort for exploring treatment strategies for diffuse astrocytoma with *IDH*-wt/*TERT*p-mut to date. Although the findings require validation in a larger cohort, they are nonetheless a promising indication that CRT might be a treatment of choice for this specific patient group.

Further, using multivariate analysis, we identified female sex as an independent prognostic factor for OS. Recent studies [25] have suggested that being female is associated with better outcome from GBM in both adults and children. Further, standard therapy is more effective in female than in male GBM patients [26], consistently with our findings.

MGMTp methylation in malignant glioma suggests a better response to treatment compared with malignant glioma with unmethylated *MGMT*p [27]. Arita et al. [28] investigated the association between *TERT*p-mut and *MGMT*p methylation on survival of patients with GBM (n = 453). A multivariate Cox regression model revealed a significant interaction for OS between these genetic markers (P = 0.0064). The benefit of *MGMT*p methylation was most pronounced in *TERT*p-mut-only tumors. Some reports on *IDH*-wt grade III gliomas strongly suggest a predictive effect for benefit from chemotherapy for patients with methylated *MGMT*p [29,30]. By contrast, in the current study, 4 of 10 CRT group patients with *MGMT*p methylation died, while only 1 of 9 patients with unmethylated *MGMT*p died. However, the limited sample size precluded subgroup analysis. The predictive value of *MGMT*p methylation of benefitting from alkylating agent chemotherapy in patients with *IDH*-wt/*TERT*p-mut grade II/III gliomas deserves further investigation.

In addition to the relatively small sample size, several possible factors may have confounded data interpretation. First, patient assignment into CRT and RT groups may have inadvertently affected the outcome. However, that was unlikely since we showed that factors such as age, pathologic classification, and total resection were not different between the two groups, and did not affect OS. Second, the salvage therapy was mainly administered to the CRT group. This was necessary as the patients in the RT group progressed too quickly to be administered salvage therapy. The fact that the CRT group patients with tumor recurrence had more chance to receive salvage treatment also support the benefits of CRT over RT. Overall, although the major conclusions of the study should be verified with a larger sample size, the findings of the current study are highly encouraging. In conclusion, we showed that patients treated with RT concurrent with daily TMZ followed by adjuvant TMZ for newly diagnosed *IDH*-wt/*TERT*p-mut grade II/III gliomas had significantly better OS than patients in the RT group. Furthermore, female sex was a significant favorable prognostic factor in this LGG subgroup. This initial study is an encouraging prerequisite for a large multi-center prospective randomized trial to validate these findings.

Note

Clinical trial information: NCT02766270.
This trial was registered on the clinicaltrials.gov (NCT02766270) prior to patient enrollment.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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