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ORIGINAL ARTICLE

Observation versus radiotherapy with or without temozolomide in postoperative WHO grade II high-risk low-grade glioma: a retrospective cohort study

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Abstract

The optimal adjuvant treatment of high-risk low-grade glioma (LGG) is controversial. We performed this retrospective cohort study to compare three treatments including observation, radiotherapy (RT) alone, and radiotherapy combined with concomitant and adjuvant temozolomide (TMZ) chemotherapy (STUPP regimen) in patients with high-risk LGG. Patients with high-risk (age > 40 or undergoing subtotal resection or biopsy) LGG treated with observation or radiotherapy alone or STUPP regimen after operation were retrospectively analyzed. Survival rates were evaluated by the Kaplan-Meier method; the log-rank test was applied to compare differences between groups. A total of 250 patients met the inclusion criteria. Median follow-up for living people was 70 months. Overall, patients who received radiotherapy with or without temozolomide had better progression-free survival (PFS) and overall survival (OS) when compared with observation (median PFS: observation, 59 months; RT, 82 months; STUPP, not reached; median OS: observation, 96 months; RT, not reached; STUPP, not reached), whereas STUPP regimen did not further prolong PFS or OS than RT alone (PFS, $P = 0.203$; OS, $P = 0.146$). In oligodendroglioma (IDH mutant and 1p/19q codeleted) subtype, only STUPP regimen brought longer PFS when compared with observation ($P = 0.008$). The incidence of grade 3 or 4 neutropenia ($P < 0.001$) and nausea or vomiting ($P = 0.004$) was higher in the STUPP group than the figure for the RT alone group. PFS and OS were similarly improved in patients with high-risk LGG receiving RT alone or STUPP regimen. However, only STUPP regimen was able to bring better PFS for oligodendroglioma (IDH mutant and 1p/19q codeleted) subgroup. Longer follow-up time is needed to determine an association with treatment effect in different histological and molecular subgroups.

Keywords High-risk low-grade glioma · Radiotherapy · STUPP regimen · IDH1-R132H mutation

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Introduction

Low-grade gliomas are primary cerebral tumors including grade I and II according to the WHO classification [1]. The major type of LGG in adults is grade II glioma, which accounts for about 5 to 10% of all brain tumors in adults [2]. According to the 2016 revision of WHO classification of tumors of the central nervous system, the major pathological types of grade II LGG include diffuse astrocytoma (IDH wild-type, IDH mutant or not otherwise specified) and oligodendroglioma (IDH mutant and 1p/19q codeleted or not otherwise specified) [3]. Surgery is the primary modality for LGG, and the optimal postoperative adjuvant treatment is still not unanimous. At present, adjuvant therapy modalities consist of observation, radiotherapy, chemotherapy, or chemoradiation [4]. It has been reported that immediate postoperative radiotherapy improved PFS and had better seizure control when compared with that of the observation group [5]. Furthermore, the TMZ group achieved similar PFS in high-risk LGG when compared with the RT group [6]. Meanwhile, the health-related quality of life and cognitive function (CF) did not differ between RT alone and TMZ alone either [7]. In other words, TMZ has similarly improved PFS without additional CF damage comparing with RT alone. Recently, RTOG 9802 showed an impressive improvement in both PFS (10.4 vs. 4.0 years) and OS (13.3 vs. 7.8 years) of adjuvant RT followed by PCV chemotherapy (procarbazine, lomustine, and vincristine) in postoperative patients with high-risk LGG [8, 9]. However, procarbazine, one of the PCV chemotherapeutic regimen, is not easily accessible in mainland China. Also, STUPP regimen was applied in RTOG 0424 to treat patients with high-risk LGG [10]. It unveiled that STUPP regimen had better median survival time (MST) and OS compared with historical controls that used RT alone [11, 12]. Nowadays, it's common for Chinese doctors to deliver STUPP regimen to patients with high-risk LGG after the operation in clinical practice. However, STUPP regimen still lacks evidence from clinical trials in Chinese LGG patients.

In the latest decade, different tissue types and molecular subtypes of LGG have been analyzed in a series of clinical trials. And a new method for diagnosis based on histopathology and molecular parameters is proposed. Since a few prospective clinical trials were reported in China, we attempted to analyze clinical outcomes of different adjuvant treatment in postoperative high-risk LGG patients basing on real-world data and also investigate the effect of adjuvant treatment on different histological and molecular subtypes. Our data may provide evidence for personalized decision-making in Chinese patients with LGGs and serve as the basis for prospective phases II–III LGG trials.

Methods

Patients

Between January 2008 and December 2015, patients with WHO grade II glioma, treated in four hospitals in China (West China Hospital, Sichuan University; Sichuan Provincial People's Hospital; Sichuan Cancer Hospital and Institute; Affiliated Hospital of North Sichuan Medical College) were retrospectively analyzed. Our inclusion criteria were as follows: (1) patient was confirmed with newly diagnosed WHO grade II astrocytoma or oligodendroglioma based on pathology review by neuropathologists in West China Hospital; (2) patient aged 18 to 80 with high-risk features according to the latest NCCN guidelines (over 40 years old or without total resection); (3) patient underwent observation or radiotherapy alone or STUPP regimen after operation or biopsy; (4) Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 2; (5) patient had no, mild, or moderate neurologic symptoms and signs; and (6) tumors located in supratentorial areas. The exclusion criteria included the following: (1) patient was diagnosed with pleomorphic xanthoastrocytoma, pilocytic astrocytoma, ganglioglioma, subependymal giant-cell astrocytoma, or dysembryoplastic neuroepithelial tumor; (2) gliomatosis cerebri; (3) tumors invaded the optic chiasm and/or optic nerve; (4) tumors spread to non-contiguous cranial or spinal leptomeninges; (5) patient received prior radiation therapy or systemic chemotherapy; (6) patient was diagnosed with a synchronous malignancy excluding carcinoma of the cervix in situ or non-melanoma skin cancer; and (7) patient had prior malignancy's disease-free survival less than 5 years. We used immunohistochemistry to detect the most common IDH1-R132H mutation status and fluorescence in situ hybridization (FISH) to detect 1p/19q codeletion status. Our primary outcome was PFS, which was calculated from the date of histological diagnosis to the date of first clinical or imaging reported disease progression or death. The secondary outcomes were OS and adverse events. OS was defined as the time between histological confirmation and death due to any reason.

Treatment

All patients were treated with an operation, including gross total resection (GTR), subtotal resection (STR), and biopsy. The extent of tumor resection was assessed by neuroradiologists comparing preoperative and postoperative MRI. The observation group received surgery only. The RT group and the STUPP group received the same intensity-modulated radiation therapy (IMRT) after the operation. A total radiotherapy dose of 50–54 Gy was given in 25–30 fractions (1.8–2.0 Gy once daily, 5 days per week). Concurrent chemotherapy of STUPP regimen was oral TMZ, 75 mg/m^2 per day, during

radiation therapy. Adjuvant chemotherapy of STUPP regimen began on the 28th day after radiotherapy, which consisted of six cycles of TMZ, 150 to 200 mg/m^2 per day for five consecutive days, repeated every 4 weeks. Salvage treatments, including reoperation, RT alone, TMZ alone, and RT plus TMZ, were given as disease progressed.

Follow-up

During adjuvant treatment, complete blood count (CBC), serum biochemistry, and physical examination were examined weekly for toxicity. Comprehensive evaluations included cranial magnetic resonance imaging (MRI), physical examination, and blood and chemistry tests, and they were carried out 4 weeks after the completion of radiotherapy, every 3 months in the first 2 years, every 6 months from 3 to 5 years and at least annually thereafter. Treatment-related toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.03).

Statistical analysis

Statistical analysis was performed via the SPSS version 22.0 software (IBM). A P value < 0.05 was considered statistically significant when we compared three groups together, and Bonferroni-adjusted P value < 0.0167 was considered statistically significant when we compared any two of the three groups. The chi square test, continuity correction, and Fisher exact test were used to compare the baseline characteristics and the incidence of adverse events between groups. The outcomes including PFS and OS were calculated by the Kaplan-Meier method, and the log-rank test was used to compare survival curves between groups [13]. The Cox proportional hazard analysis was carried out to estimate the HR associated with outcomes and to identify the independent prognostic factors by multivariate analysis.

Results

Clinical characteristics

Among 646 patients diagnosed with WHO grade II glioma, 250 patients met criteria for inclusion between 2008 and 2015. Median follow-up for all patients still alive was 70 months (range 39–131 months), and the median follow-up for the observation group, the RT group, and the STUPP group was 82 months, 75 months, and 58 months, respectively. Among 250 eligible patients, the majority of them received RT alone (n = 106, 42.4%), and 83 patients (33.2%) underwent observation, whereas fewer patients were treated with STUPP regimens (n = 61, 24.4%). The rates of subtotal resection or biopsy in the RT group and the STUPP group were 87.7% and 93.4% respectively, and 80.7% of patients in the observation group received incomplete resections. Patients' age, gender, histology, and performance status were well-balanced between groups (Table 1). Molecular markers including IDH1-R132H mutation status, 1p/19q codeletion status, and MGMT promoter methylation status were evaluated. Among the included 250 patients, 137 patients were tested for IDH1-R132H mutation status, and 64 patients were tested for 1p/19q codeletion status, and 62 patients were tested for MGMT promoter methylation status. IDH1-R132H mutation was detected in 96 of 137 patients and 1p/19q codeletion was detected in 48 of 64 patients, with 43 patients having both IDH1-R132H mutation and 1p/19q codeletion. MGMT promoter methylation was detected in 48 of 62 patients.

Treatment outcomes

After a median follow-up of 70 months (39–131 months), progression events occurred in 110 patients in all (observation, 53; RT, 43; RT + TMZ, 14), and 59 of all 250 patients died (33 in the observation group, 21 in the RT group, and 5 in the RT + TMZ group). The median PFS time for the observation group was 59 months and for radiotherapy alone 82 months. The STUPP group did not reach its median PFS time. Overall, patients who received radiation therapy with or without temozolomide had better PFS than the observation group (RT vs observation, unadjusted HR, 0.536; 95% CI, 0.358 to 0.803; log-rank P = 0.002; RT + TMZ vs observation, unadjusted HR, 0.354; 95% CI, 0.196 to 0.639; log-rank P < 0.001). But there was no difference between the RT group and the STUPP group (RT vs RT + TMZ, unadjusted HR, 1.517; 95% CI, 0.828 to 2.780; log-rank P = 0.203) (Fig. 1a). The median OS time for observation, RT alone, and STUPP arm was 96 months, not reached and not reached, respectively. When compared with observation, both RT alone and STUPP regimen were associated with improved OS (RT vs observation, unadjusted HR, 0.485; 95% CI, 0.281 to 0.840; log-rank P = 0.009; RT + TMZ vs observation, unadjusted HR, 0.243; 95% CI, 0.094 to 0.628; log-rank P = 0.002), whereas STUPP regimen did not further prolong OS than RT alone (RT vs RT + TMZ, unadjusted HR, 1.994; 95% CI, 0.749 to 5.310; log-rank P = 0.146) (Fig. 1b).

Subgroup analysis

More than half of participants were diagnosed with astrocytoma (172), in contrast to 78 patients who were diagnosed with oligodendroglioma. Considering histological types of LGGs, when compared with observation, RT alone prolonged PFS and OS in patients diagnosed with astrocytoma (PFS: RT vs observation, unadjusted HR, 0.552; 95% CI, 0.345 to 0.883; log-rank P = 0.012; OS: RT vs observation, unadjusted HR, 0.431; 95% CI, 0.230 to 0.808; log-rank P = 0.007), and so did

Table 1 Baseline characteristics of patients

Characteristic	Overall (n = 250)	Observation (n = 83)	RT alone (n = 106)	RT + TMZ (n = 61)	P value
Age (years)					0.116
≤ 40	132 (52.8%)	39 (47.0%)	54 (50.9%)	39 (63.9%)	
> 40	118 (47.2%)	44 (53.0%)	52 (49.1%)	22 (36.1%)	
Gender					0.980
Male	138 (55.2%)	46 (55.4%)	59 (55.7%)	33 (54.1%)	
Female	112 (44.8%)	37 (44.6%)	47 (44.3%)	28 (45.9%)	
Histology					0.458
Astrocytoma	172 (68.8%)	61 (73.5%)	72 (67.9%)	39 (63.9%)	
Oligodendroglioma	78 (31.2%)	22 (26.5%)	34 (32.1%)	22 (36.1%)	
Extent of resection					0.078
Gross total	33 (13.2%)	16 (19.3%)	13 (12.3%)	4 (6.6%)	
Subtotal or biopsy	217 (86.8%)	67 (80.7%)	93 (87.7%)	57 (93.4%)	
Performance status					0.085
ECOG 0-1; ECOG 2	233 (93.2%); 17 (6.8%)	73 (88.0%); 10 (12.0%)	101 (95.3%); 5 (4.7%)	59 (96.7%); 2 (3.3%)	

RT radiotherapy, *TMZ* temozolomide, *ECOG* Eastern Cooperative Oncology Group

STUPP regimen (PFS, RT + TMZ vs observation, unadjusted HR, 0.445; 95% CI, 0.233 to 0.850; log-rank P = 0.010; OS, RT + TMZ vs observation, unadjusted HR, 0.167; 95% CI, 0.050 to 0.551; log-rank P = 0.001). But there was no difference between RT alone and STUPP regimen (PFS: RT vs RT + TMZ, unadjusted HR, 1.242; 95% CI, 0.636 to 2.424; log-rank P = 0.564; OS: RT vs RT + TMZ, unadjusted HR, 2.585; 95% CI, 0.746 to 8.949; log-rank P = 0.088) (Fig. 2c, 2d). In oligodendroglioma (IDH mutant and 1p/19q codeleted), people who received STUPP regimen got better PFS than observation (RT + TMZ vs observation, unadjusted HR, 0.109; 95% CI, 0.013 to 0.890; log-rank P = 0.008), while no statistic difference was achieved between the RT group and the observation group in terms of PFS (RT vs observation, unadjusted HR, 0.531; 95% CI, 0.177 to 1.589; log-rank P = 0.261). Besides, PFS in the STUPP group was similar to RT alone (RT vs RT + TMZ, unadjusted HR, 4.872; 95% CI, 0.581 to 40.877; log-rank P = 0.171) in this population (Fig. 3e). Differences in OS among three groups were not significant (overall comparison P = 0.927; RT vs observation, P = 0.957; RT + TMZ vs observation, P = 0.584; RT vs RT + TMZ, P = 0.817) (Fig. 3f). Considering molecular subtype of LGGs, patients with IDH1-R132H mutation treated with RT or STUPP regimen obtained better PFS than those treated with observation (RT vs observation: unadjusted HR, 0.319; 95% CI, 0.157 to 0.649; log-rank P = 0.001; RT + TMZ vs observation: unadjusted HR, 0.257; 95% CI, 0.101 to 0.653; log-rank P = 0.002). But STUPP regimen did not further improve PFS than RT alone in this population (RT vs RT + TMZ, unadjusted HR, 1.239; 95% CI, 0.465 to 3.300; log-rank P = 0.753) (Fig. 4g). With regard to OS, neither radiotherapy alone nor STUPP regimen could bring better survival outcomes for patients with IDH1-R132H mutation (RT vs observation: unadjusted HR, 0.702; 95% CI, 0.244 to 2.018; log-

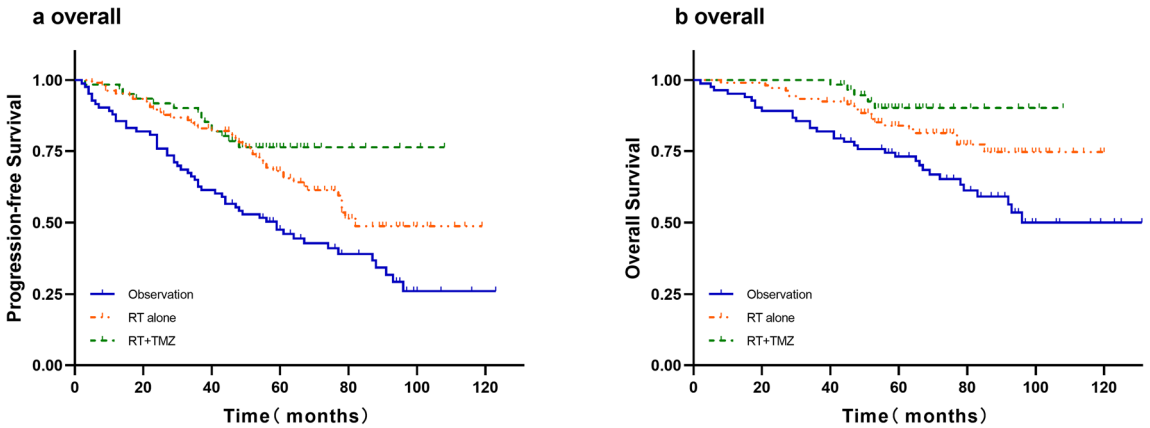

Fig. 1 Progression-free survival (**a**) and overall survival (**b**) for all patients according to the treatment group. Abbreviations: RT, radiotherapy; TMZ, temozolomide

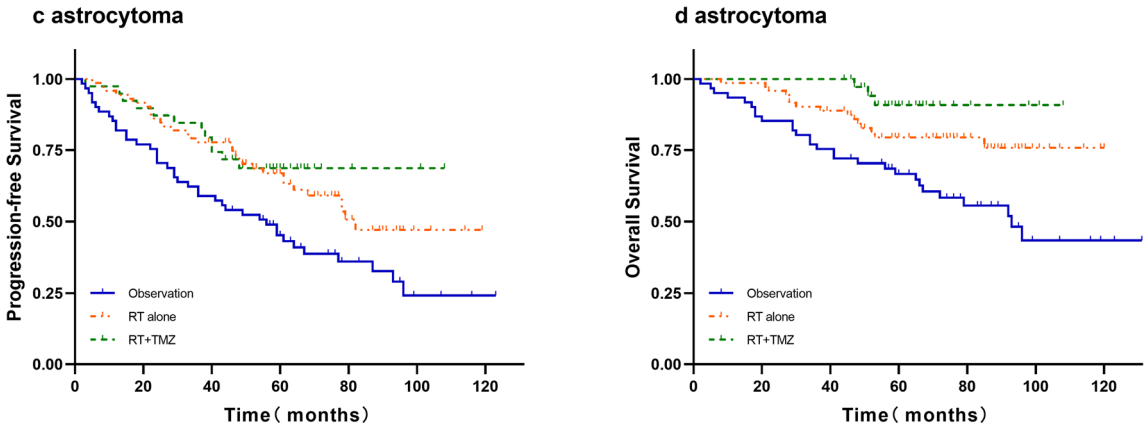

Fig. 2 Progression-free survival (**c**) and overall survival (**d**) for patients with astrocytoma according to the treatment group. Abbreviations: RT, radiotherapy; TMZ, temozolomide

rank $P = 0.514$; RT + TMZ vs observation: unadjusted HR, 0.438; 95% CI, 0.086 to 2.223; log-rank $P = 0.304$) (Fig. 4h).

To identify the independent prognostic factors, age, histology, treatment modality, and molecular type (IDH1-R132H mutant status, MGMT promoter methylation status) were included in multivariate analysis. The Cox proportional hazard analysis exhibited that treatment modality, IDH1-R132H mutant status and MGMT promoter methylation status were significantly associated with PFS (Table 2).

Adverse events

A total of 51 (83.6%) patients completed six cycles of adjuvant temozolomide. Two patients quit due to tumor progression, seven patients terminated on account of grade 4 neutropenia, and one patient because of grade 3 non-hematologic adverse event. The most commonly observed grade 3 or 4 hematologic toxicity in the STUPP group was neutropenia, which occurred in 16 (26.2%) patients. No grade 3 or 4 hematologic toxic effects were recorded in the RT alone group. The most frequent non-hematologic toxicity in the RT alone group was cognitive disorders, which took place in 8 (7.5%) patients. The most common non-hematologic toxicity in the STUPP group was nausea or vomiting, which documented in 9 (14.8%) patients. The incidence of grade 3 or 4 neutropenia ($P < 0.001$) and nausea or vomiting ($P = 0.004$) was higher in the STUPP group than the figure for the RT alone group. No statistical difference was observed in other grade 3 or 4 adverse events between these two groups (Table 3).

Discussion

Postoperative adjuvant therapy for LGG is still controversial. Radiotherapy followed by PCV is able to improve the prognosis of high-risk LGG. However, procarbazine is unavailable in mainland China, and the data of STUPP regimen for LGG is deficient in China.

Several observations have been made in our study. Patients with high-risk LGG who received adjuvant therapy, either radiotherapy alone or radiation combined with temozolomide chemotherapy, had better PFS and OS than those who did not. Though there was a trend towards longer PFS and OS in the STUPP group, the survival outcomes between the STUPP

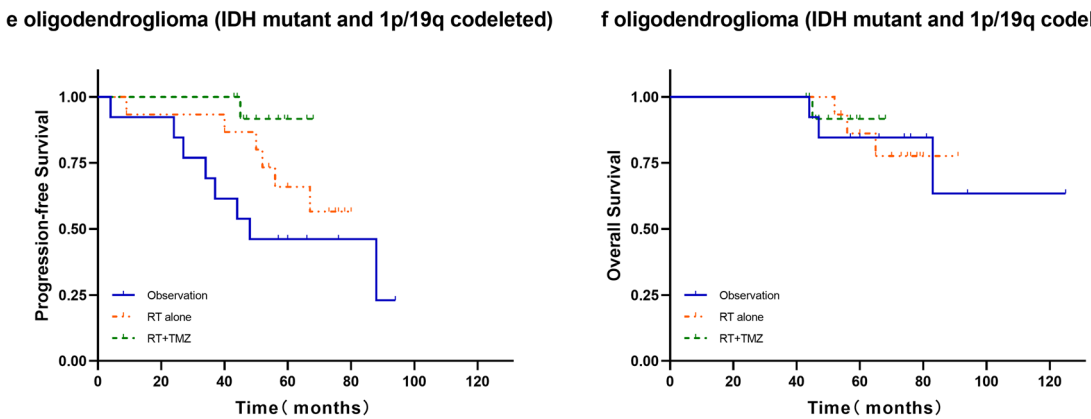

Fig. 3 Progression-free survival (**e**) and overall survival (**f**) for patients with oligodendroglioma (IDH mutant and 1p/19q codeleted) according to the treatment group. Abbreviations: RT, radiotherapy; TMZ, temozolomide; IDH, isocitrate dehydrogenase

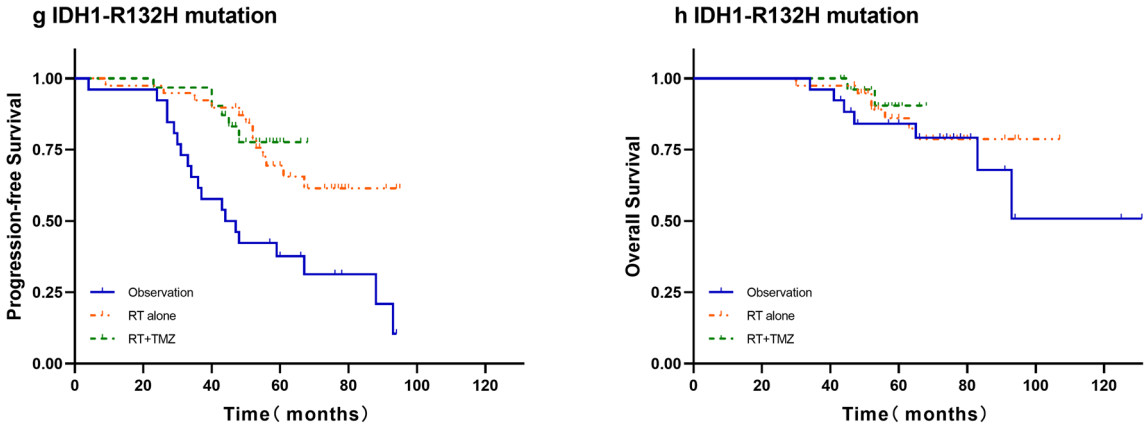

Fig. 4 Progression-free survival (**g**) and overall survival (**h**) for patients with IDH1-R132H mutation according to the treatment group. Abbreviations: RT, radiotherapy; TMZ, temozolomide

group and the RT group were not statistically significant. The absence of a statistically significant treatment effect between these two groups was partly caused by too few events for statistical analysis. Only 110 events occurred in 250 patients (44%) with only 14 events in the STUPP group (12.7% of overall events). In terms of histological and molecular subtypes, astrocytoma could benefit from not only the RT alone group but also the STUPP group in PFS and OS. While oligodendroglioma (IDH mutant and 1p/19q codeleted) could only benefit from combined chemoradiation therapy in PFS. There were no statistical differences in OS among three arms in this subgroup. Patients with IDH1-R132H mutation could acquire significantly improved PFS when treated with radiation therapy with or without temozolomide. Concerning OS, no distinct advantage was shown in three groups in this population. The outcomes of histological subgroups were in contrast to RTOG 9802 long-term results. There are several possible explanations. Firstly, we used TMZ instead of PCV as adjuvant therapy. It is not clear whether TMZ and PCV work equally well. Another cause is that the number of events was too small for statistical consideration, especially in the STUPP group, which also prevented us from finding a signal in OS in IDH-mutated patients. Besides, there existed an inherent selection bias due to the retrospective study. And 45.2% of patients had unknown IDH status because of the degradation of tumor samples, which limited our ability to reclassify them more accurately.

Temozolomide concomitantly with and after radiotherapy, namely STUPP regimen, was associated with better PFS and OS for glioblastoma [14]. Moreover, adjuvant PCV chemotherapy plus radiotherapy could prolong PFS in anaplastic glioma [15–17]. Hence, adjuvant chemoradiotherapy was worthy of clinical recommendation in high-grade glioma. However, as for low-grade glioma, the mode of postoperative adjuvant therapy remains debatable. Over the last two decades, a series of clinical trials have studied various issues in order to establish the standard management of LGG. The EORTC 22845 trial demonstrated that postoperative adjuvant radiotherapy in patients with LGG increased the median PFS by nearly 2 years than observation (5.3 years vs 3.4 years) [5]. The addition of PCV to radiotherapy for low-grade glioma was also verified in several studies. The long-term results of RTOG 9802 showed striking survival improvements for high-risk LGGs treated with adjuvant RT followed by PCV

Table 2 Multivariate analysis on progression-free survival

Prognostic factors	Hazard ratio	95% CI	*P* value
Treatment			
RT vs observation	0.175	0.062–0.496	0.001
STUPP vs observation	0.089	0.017–0.464	0.004
Age (> 40 vs ≤ 40)	2.965	0.937–9.384	0.065
Histology (OD vs astrocytoma)	2.761	0.773–9.855	0.118
Molecular marker			
IDH mutation vs IDH wild-type	0.186	0.044–0.783	0.022
MGMT promoter methylation vs non-methylation	0.221	0.062–0.785	0.020

RT radiotherapy, *STUPP* radiotherapy combined with concomitant and adjuvant temozolomide, *OD* oligodendroglioma, *IDH* isocitrate dehydrogenase, *MGMT* O-6-methylguanine-DNA methyltransferase, *CI* confidence interval

Table 3 Frequency of treatment-related grades 3–4 adverse events

Event	RT alone (n = 106)	RT + TMZ (n = 61)	P value
Neutropenia	0 (0.0%)	16 (26.2%)	< 0.001
Thrombocytopenia	0 (0.0%)	2 (3.3%)	0.132
Liver dysfunction	0 (0.0%)	1 (1.6%)	0.365
Fatigue	3 (2.8%)	4 (6.6%)	0.260
Nausea/vomiting	2 (1.9%)	9 (14.8%)	0.004
Cognitive disorders	8 (7.5%)	4 (6.6%)	1.000
Total	13 (12.3%)	36 (59.0%)	< 0.001

RT radiotherapy, *TMZ* temozolomide

chemotherapy [9]. With relatively slighter toxicity than the PCV regimen, temozolomide has become widely used and has been confirmed to have similar improved PFS to radiation [6]. In our study, the effect of adjuvant radiotherapy was further emphasized, which was in line with EORTC 22845. Nevertheless, neither in general nor in the subgroup, STUPP regimen did not display superiority in PFS or OS than RT alone. It may due to the fact that low-grade gliomas were well-differentiated gliomas and had a relatively good prognosis, it was hard to make the survival curves diverge within a short time. The median follow-up time in our study was 5.83 years, which was similar to the initial results of RTOG 9802 (5.9 years). Only after more than 10 years follow-up did the survival curves of RTOG 9802 study diverge significantly. In addition, fewer than half of patients in our study in the STUPP group and the RT group have progressed or died. Longer follow-up time is needed for further data maturation and to determine whether or not the combination of radiation and TMZ is superior to radiation alone.

Recent advances in subclassifying gliomas into molecular subgroups are based on an integrative diagnostic approach [18]. According to the newest WHO classification, patients with IDH mutation and 1p/19q codeletion are diagnosed with oligodendroglioma (IDH mutant and 1p/19q codeleted). In our study, IDH mutant and 1p/19q codeleted subgroup and oligodendroglioma subgroup could only benefit from STUPP regimen in regard to PFS. That is to say, the effect of different treatments on the prognosis of patients with IDH mutant and 1p/19q codeleted is the same as oligodendroglioma. So we considered that these two subgroups were the same, and we decided to analyze these two subgroups together. For patients with IDH mutation and 1p/19q non-codeletion, we did ATRX expression and TP53 mutant status test, and an integrated diagnostic approach was performed to identify the subtype of LGG according to the 2016 WHO criteria. Additionally, IDH mutation and 1p/19q codeletion were found to be important prognostic factors and were considered to be related to increased sensitivity to chemotherapy [19–22]. Therefore, it is reasonable that oligodendroglioma (IDH mutant and 1p/19q codeleted subgroup in our study could only gain statistically better PFS when TMZ was delivered. However, not all patients in our study were analyzed in regard to IDH1-R132H status and 1p/19q codeletion status. We missed 113 patients' IDH status, and their diagnoses were based on histology and imaging. Despite being evaluated by neuropathologists and neuroradiologists, we may have missed some patients with IDH wild-type gliomas that were in reality molecularly high-grade gliomas, and this cohort definitely had a worse prognosis. We will extend the follow-up time to include more patients with clear molecular characteristics and report our long-term results.

MGMT is a DNA-repair enzyme, and the expression of it in tumor tissues is associated with resistance to alkylating chemotherapy. Moreover, MGMT promoter methylation status is the main factor determining the expression level of MGMT which may affect the effect of chemotherapy and the prognosis of patients with glioma. A randomized clinical trial comparing RT alone with the STUPP regimen concluded that glioblastoma with MGMT promoter methylation benefited from TMZ [23]. NOA-04 showed that patients with anaplastic glioma containing MGMT promoter methylation were associated with longer PFS when treated with either radiotherapy alone or PCV or TMZ chemotherapy [24]. It is regrettable that the number of patients with MGMT promoter methylation in our current study was too small to distribute them over IDH mutant and IDH wild-type group. A larger sample size is needed to further explore the role of different molecular features in clinical decision-making.

Though this is the first study in China to assess the STUPP regimen combined with histology and molecular types in high-risk LGG, our study is subject to the limitations of retrospective data analysis and non-randomized. For example, the baseline characteristics of our patients had no statistical difference among three groups or between any two groups, but a large proportion (63.9%) of patients who received STUPP protocol were under 40. It may be a selection bias as younger patients were treated more aggressively. Another limitation is that 50% of the patients did not progress and the majority of them were still alive, which led to the failure to observe the difference of therapy effects between the RT group and the RT + TMZ group. It is necessary to prolong follow-up time to increase the number of progression and death events for PFS and OS analysis.

Conclusions

PFS and OS were improved in patients with high-risk LGG receiving radiotherapy with or without TMZ post-operation. Whereas in oligodendroglioma (IDH mutant and 1p/19q codeleted) subtype, only STUPP regimen could bring longer PFS when compared with observation. A higher incidence of grade 3 or 4 adverse events was recorded in the STUPP group.

Longer follow-up time is needed for analysis of long-term survival outcomes.

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Authors' contributions Xingchen Peng, Yanhui Liu, Jingjing Wang, Lvjun Yan, and Ping Ai contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Jingjing Wang, Ping Ai, Yanhui Liu, Yan He, Hui Guan, Zhigong Wei, Ling He, and Xiaoli Mu. The first draft of the manuscript was written by Jingjing Wang, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study has been approved by the West China Hospital, Sichuan University, Human Research Ethics Committee. All procedures in this study involving human participants were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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

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