Original Article

Association of high-dose radiotherapy with improved survival in patients with newly diagnosed low-grade gliomas

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BACKGROUND: The radiation dose for patients with low-grade gliomas (LGGs) is controversial. The objective of this study was to investigate the impact of the radiation dose on survival for patients with LGGs and especially for molecularly defined subgroups. **METHODS:** Three hundred fifty-one patients with newly diagnosed LGGs from the multicenter Chinese Glioma Cooperative Group received postoperative radiotherapy (RT) in 2005-2018. The RT dose, as a continuous variable, was entered into a Cox regression model using penalized spline regression to allow for a nonlinear relationship between the RT dose and overall survival (OS) or progression-free survival (PFS). Inverse probability of treatment weighting (IPTW)–adjusted propensity scores were used to correct for potential confounders. Dose effects on survival within *IDH* mutation and 1p/19q codeletion defined subgroups were analyzed. **RESULTS:** The risk of mortality and disease progression decreased sharply until 54 Gy. High-dose RT (≥54 Gy) was associated with significantly better 5-year OS (81.7% vs 64.0%; hazard ratio [HR], 0.33; $P < .001$) and PFS (77.4% vs 54.5%; HR, 0.46; $P < .001$) than low-dose RT (<54 Gy). IPTW correction confirmed the associations (HR for OS, 0.44; $P = .001$; HR for PFS, 0.48; $P = .003$). High-dose RT was associated with longer PFS (HR, 0.25; $P = .002$; HR, 0.21; $P = .039$) and OS (HR, 0.27; $P = .006$; HR, 0.07; $P = .017$) in *IDH*-mutant/1p/19q noncodeleted and *IDH* wild-type subgroups, respectively. No significant difference in survival was observed with high-dose RT in the *IDH*-mutant/1p/19q codeleted subgroup. **CONCLUSIONS:** High-dose RT (≥54 Gy) was effective in LGGs. Patients with an *IDH* mutation/1p/19q noncodeletion or *IDH* wild-type may need to be considered for high-dose RT. ***Cancer* 2022;128:1085-1092**.

LAY SUMMARY:

- The radiotherapy dose-response was observed in patients with low-grade gliomas, and high-dose radiotherapy (≥54 Gy) was associated with improved survival.
- Patients with an *IDH* mutation/1p/19q noncodeletion or wild-type *IDH* may have improved survival with the administration of high-dose radiotherapy.

KEYWORDS: low-grade gliomas, molecular subgroups, overall survival, progression-free survival, radiation dose.

INTRODUCTION

Low-grade gliomas (LGGs) are generally World Health Organization (WHO) grade 2 astrocytomas and oligodendrogliomas. They are rare, aggressive, and heterogeneous tumors with highly variable outcomes. Based on different risk factors, the 5-year survival rate for patients with LGGs ranges from 49% to 93%.[1-5] Because of their aggressive behavior, malignant transformation, and high recurrence rate, postoperative radiotherapy (RT) has often been used in their management. Several prospective and retrospective studies have confirmed that postoperative RT can provide a benefit to patients with LGGs by controlling symptoms, delaying recurrence, and prolonging survival.[6-8] However, the RT dose is the most common controversial topic in clinical practice. A dose-response relationship has been established in glioblastoma (WHO grade 4).[9,10] Unfortunately, it is difficult to conduct studies on the RT dose for LGGs because of the requirements for long-term follow-up. Earlier retrospective studies have shown an improvement in survival associated with an increasing RT dose,[11-14] but a dose-response from comparisons of 2 doses (45 vs 59.4 Gy or 50.4 vs 64.8 Gy) was not observed in 2 randomized phase 3 clinical trials.[15,16] However, it is important to mention that these 2 studies were activated in 1985 and 1986 and had many limitations in both diagnostic

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technology (computed tomography [CT]) and radiation modalities (2-dimensional planning). New trials should be designed that are based on modern technology, such as magnetic resonance imaging (MRI), intensity-modulated radiation therapy (IMRT), and especially molecular pathological diagnosis. To date, there are no reports on the relationship between the RT dose and the specific molecular subgroups of LGGs.

The isocitrate dehydrogenase 1/2 mutation (*IDH* mutation) and the chromosome arm 1p/19q codeletion (1p/19q codeletion) are the most common molecular alterations in gliomas.[17,18] Improved survival is associated with the *IDH* mutation or 1p/19q codeletion according to prospective and retrospective studies.[19-21] Radiation Therapy Oncology Group (RTOG) 9802 was the first to demonstrate a survival benefit of adjuvant chemoradiotherapy over RT in high-risk patients with *IDH*-mutant LGGs, regardless of their 1p/19q codeletion status.[20] However, the values of these molecular markers for radiation doses have not been reported to date.

In this study, the RT dose was examined as a continuous variable for its association with survival in LGGs. Because of the uncertainties regarding the optimal dose, we used modern statistical methods in a large cohort of LGGs to evaluate the effects of the RT dose on survival. We analyzed the potential survival benefits of high-dose RT in patients with specific molecular subgroups. Our findings provide evidence for making treatment decisions and designing clinical trials for LGGs.

METHODS AND MATERIALS

Patient Population

The molecular data and follow-up information for 351 patients with newly diagnosed adult supratentorial LGGs (WHO grade 2) were obtained from the multicenter Chinese Glioma Cooperative Group and the Chinese Glioma Genome Atlas in China in 2005-2018. Patients were treated at Beijing Tiantan Hospital, Sanbo Brain Hospital, Tianjin Medical University General Hospital, the First Affiliated Hospital of Nanjing Medical University, Harbin Medical University, and China Medical University (http://www.cgga.org.cn/). Tumor histology was confirmed independently by 2 neuropathologists on the basis of the 2007 WHO classification and the 2016 updated edition. For molecular pathology, pyrosequencing for the *IDH* mutation and fluorescence in situ hybridization for the 1p/19q codeletion were performed according to our previous studies.[21,22] The study was approved by the ethics review board of Tiantan Hospital in Beijing, China. Written informed consent was obtained from all participants. The patients had to be in good general condition as indicated by their performance score after surgery (Karnofsky performance scores ≥ 70). Patient characteristics (stratified by the RT dose) are summarized in Supporting Table 1.

Treatments

All patients underwent surgical excision. The extent of resection was evaluated with preoperative and postoperative MRI. Removal of <90% of the tumor was defined as subtotal. All patients underwent postoperative 3-dimensional conformal radiotherapy or IMRT. The radiation fields were based on the postoperative T2 or fluid-attenuated inversion recovery MRI–defined residual tumor and/or surgical cavity plus a 2-cm margin. The median dose was 55.8 Gy (range, 40-66 Gy; 1.8-2.0 Gy daily, 5 days per week). The distribution of doses in patients with LGGs is shown in Supporting Figure 1. All patients received RT 4 to 12 weeks after surgery. A total of 31.1% of the patients (105 of 338) received RT followed by chemotherapy using carmustine, nimustine, or temozolomide. In the first 2 years, follow-up and MRI were performed after RT every 6 months, and they were performed every 9 to 12 months thereafter until tumor progression.

Statistical Analyses

The clinical features of the different subgroups were compared with the χ^2 test with SPSS v22.0 (IBM, Armonk, New York). Survival was calculated with the Kaplan-Meier method. Overall survival (OS) was calculated from the day of surgery to the date of the first event. The date of progression was defined as the date of the CT or MRI examination that confirmed progression or related neurologic symptoms. Logistic regression was used to calculate propensity scores from baseline patient characteristics, including age, sex, histopathology, resection level, and chemotherapy. Inverse probability of treatment weighting (IPTW) analysis based on propensity scores was performed to assess progression-free survival (PFS) and OS between cohorts. Cox proportional hazards regression was used to identify independent risk factors for OS and PFS. Multivariate analyses used the stepwise likelihood ratio method, and all covariates (age, sex, histopathology, resection, chemotherapy, RT dose, *IDH* mutation, and 1p/19q codeletion) were entered and analyzed. Subgroups were compared with the log-rank test. $P < .05$ (2-sided) was considered to indicate statistical significance.

The penalized spline (P-spline) that was fit into the Cox model allowed a nonlinear relationship between the RT dose and the logarithm of the hazard ratio (HR) for tumor progression or mortality. We used the degrees of

freedom in the multivariate additive Cox models (dfmacox) function in smoothHR within R v3.2.3 (R Institute for Statistical Computing, Vienna, Austria [https://www.r-project.org/]) to obtain the optimal number of degrees of freedom in the extended Cox-type additive hazard regression model. P-spline was performed with the smoothHR package in R v3.2.3.

RESULTS

Patient Characteristics

The cohort comprised 351 patients with LGGs at 6 institutions in China between 2005 and 2018. The median age was 38 years (range, 11-69 years), and the male-to-female ratio was 1.4:1 (207:144). The median follow-up time was 8.8 years (95% confidence interval [CI], 7.8-9.7 years). There were 99 deaths (72 of 284 [25.3%] in the high-dose group and 27 of 67 [40.3%] in the low-dose group) and 120 recurrences (88 of 284 [31.0%] in the high-dose group and 32 of 67 [47.8%] in the low-dose group) to date. The 5-year OS and PFS rates for all patients were 78.3% and 73.0%, respectively. Unweighted and weighted baseline characteristics of the patients are reported in Supporting Table 1.

Dose-Response of RT on Survival

To quantify the dose-response relationship, we entered the RT dose as a continuous variable into the Cox regression by using P-splines in smoothHR to allow for nonlinear relationships between the RT dose and survival. This model demonstrated that the risk of death decreased sharply until 54 Gy and then no longer significantly declined (Fig. 1A), whereas the risk of tumor progression continued to decline with radiation dose escalation (Fig. 1B). Depending on the dose of 54 Gy, we divided patients into 2 groups: high dose (≥54 Gy; 284 patients) and low dose (<54 Gy; 67 patients). The rates of 5-year OS (81.7% vs 64.0%; HR, 0.33; 95% CI, 0.28-0.67; $P < .001$) and PFS (77.4% vs 54.5%; HR, 0.46; 95% CI, 0.30-0.69; $P < .001$) were significantly higher in the high-dose group than the low-dose group (Fig. 2A,B). IPTW-adjusted Kaplan-Meier curves showed similar results in OS (HR, 0.44; $P = .001$) and PFS (HR, 0.48; $P = .003$; Fig. 2C,D). After IPTW adjustments (age, sex, histopathology, extent of resection, and chemotherapy), all standardized mean differences were <10% (Supporting Table 1). In addition, the data for the 351 patients were split into discovery and validation sets by time: the discovery data set from 2005 to 2009 (199 [56.7%]) and the validation data set from 2010 to 2018 (152 [43.3%]). High-dose RT for

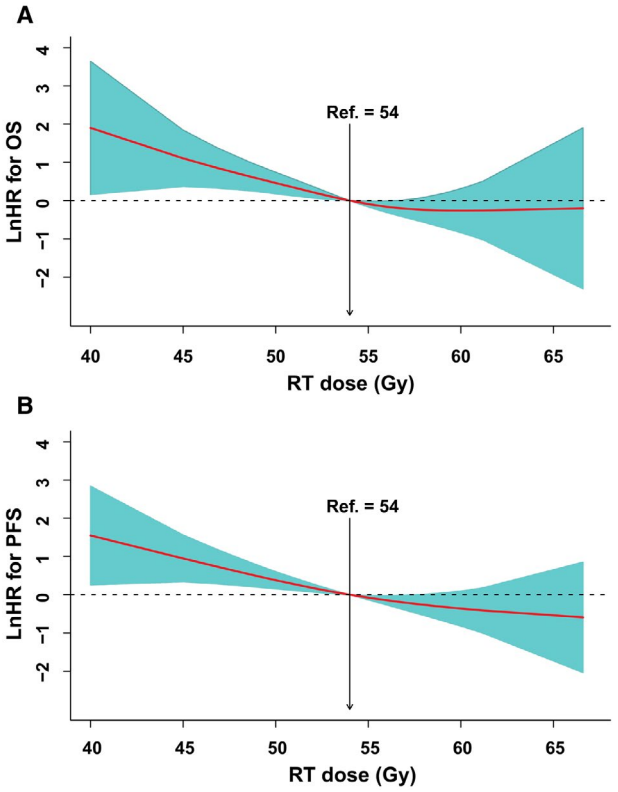

Figure 1. Dose-response of RT with respect to survival outcomes. Estimated logarithm HRs (red lines) along with 95% confidence intervals (shading) for the association between RT dose and PFS and OS in 351 patients based on the dfmacox function in a smoothHR optimal extended Cox-type additive hazard regression unadjusted model. The effects of the RT dose on the risk of (A) mortality and (B) tumor progression are modeled with penalized spline expansion, with the RT dose used as a continuous covariate. A dose of 54 Gy (indicated by the vertical line), as the optimal cutoff value, was used as the reference value for calculations. dfmacox indicates degrees of freedom in multivariate additive Cox models; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RT, radiotherapy.

patients with LGGs had survival benefits in the discovery set (P for OS = .009; P for PFS = .016; Supporting Fig. 2A,B), and the results were also confirmed in the validation set (P for OS = .004; P for PFS = .004; Supporting Fig. 2C,D).

Dose-Response in Molecular Subgroups

Of the 298 samples (84.9%) that underwent *IDH* analysis, 240 (80.5%) had mutations, and 58 (19.5%) were wild type. Of the 196 samples (55.8%) that underwent 1p/19q analysis, 79 (40.3%) had a codeletion, and 117 (59.7%) had no codeletion. In a univariate analysis, histopathology, RT dose, and 1p/19q codeletion were statistically significant prognostic factors for both PFS and OS

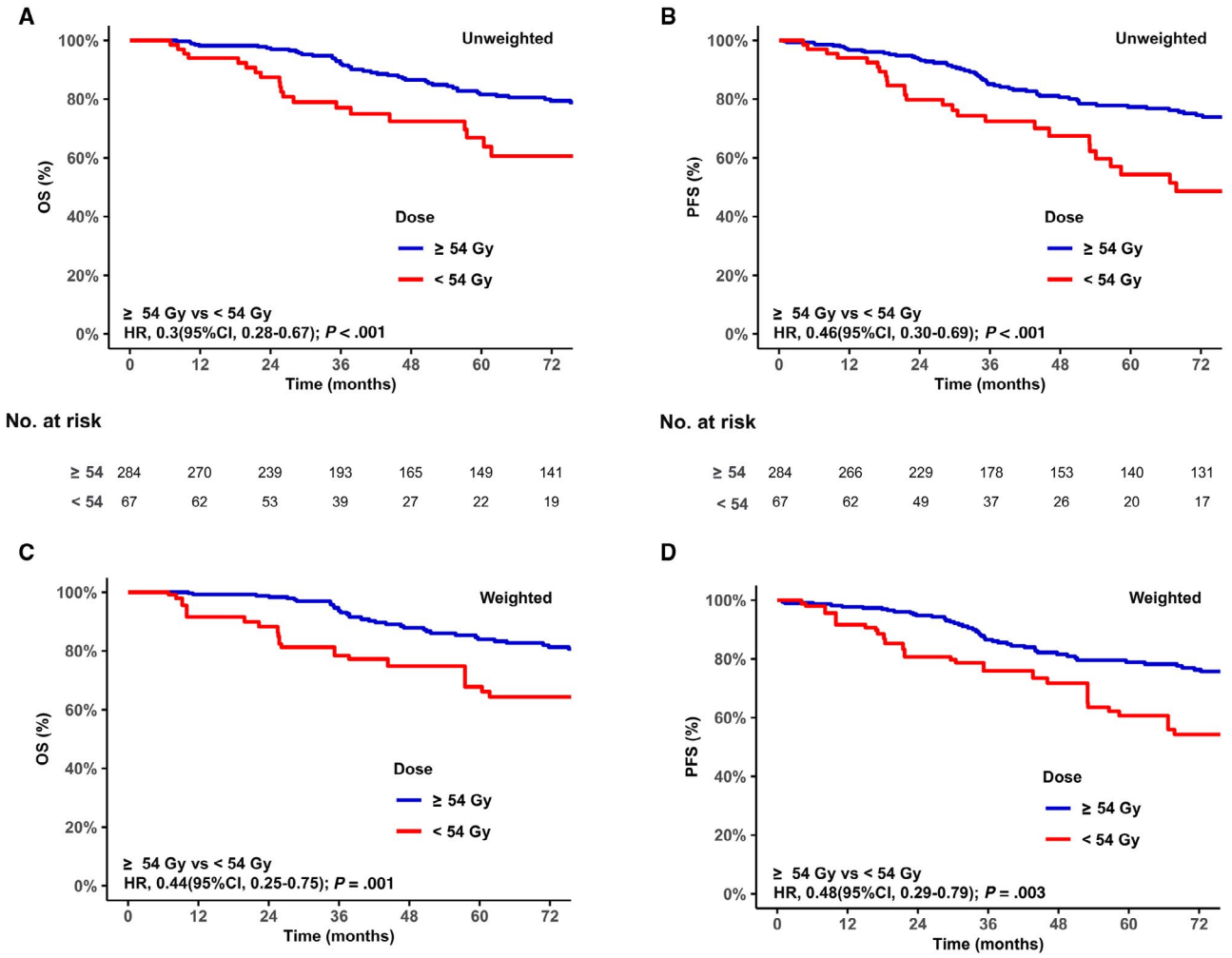

Figure 2. Patients who received RT doses ≥ 54 Gy had longer survival. The improved OS and PFS with high-dose RT were analyzed (A,B) before and (C,D) after adjustments of inverse probability of treatment weighting. CI indicates confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RT, radiotherapy.

(Table 1). In a multivariate analysis based on all covariates, high-dose RT and 1p/19q codeletion were found to be statistically significant for favorable PFS (HR for RT dose, 0.37; $P = .001$; HR for codeletion, 0.40; $P = .021$) and OS (HR, 0.40 for RT dose; $P = .004$; HR for codeletion, 0.31; $P = .002$).

Of the eligible patients successfully profiled for the *IDH* mutation and 1p/19q codeletion defined molecular groups (179 of 351) according to the 2016 WHO classification, 86 (48.0%) were *IDH*-mutant/noncodeleted, 69 (38.5%) were *IDH*-mutant/codeleted, and 24 (13.4%) were *IDH* wild-type. In agreement with the RTOG 9802 trial,[20] the 3 molecular subgroups were significantly associated with OS ($P = .004$) and PFS ($P = .0003$; Fig. 3A,B). The 5-year OS rates were 90.2% for the *IDH*-mutant/codeleted subgroup, 76.4% for the *IDH*-mutant/noncodeleted subgroup, and 59.1% for the *IDH* wild-type subgroup. The 5-year PFS rates were 89.1% for the *IDH*-mutant/codeleted subgroup, 64.2% for the *IDH*-mutant/noncodeleted subgroup, and 51.1% for the *IDH* wild-type subgroup. High-dose RT was associated with longer OS (HR, 0.27; $P = .006$) and PFS (HR, 0.25; $P = .002$) in comparison with patients treated with low-dose RT in the *IDH*-mutant/noncodeleted subgroup (Fig. 4A,B). For the *IDH* wild-type subgroup, patients treated with high-dose RT experienced longer OS (HR, 0.07; $P = .017$) and PFS (HR, 0.21; $P = .039$) in comparison with patients treated with low-dose RT (Fig. 4C,D). For the *IDH*-mutant/codeleted subgroup, there was no clinical benefit from high-dose RT (Fig. 4E,F). Most clinical characteristics were comparable between the groups (Supporting Table 2).

TABLE 1. Univariate Analyses and Multivariate Analyses for PFS and OS Based on Clinical and Molecular Variables

		Univariate Analyses						Multivariate Analyses					
		PFS			OS			PFS			OS		
Variable	No.	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age: ≤40 vs >40 y	199/152	0.72	0.50-1.03	.072	0.78	0.52-1.16	.213	0.61	0.36-1.05	.073	0.64	0.35-1.17	.148
Sex: male vs female	207/144	1.17	0.81-1.68	.403	1.05	0.70-1.57	.816	1.44	0.81-2.54	.211	1.04	0.55-1.96	.905
Histopathology: A vs O	291/60	2.65	1.39-5.06	.003	2.64	1.28-5.44	.008	2.16	0.85-5.48	.107	1.93	0.73-5.12	.187
Resection: total vs subtotal	141/171	0.79	0.53-1.19	.258	0.95	0.62-1.48	.832	1.05	0.58-1.90	.88	1.29	0.67-2.49	.446
Chemotherapy: yes vs no	105/233	1.74	1.19-2.53	.004	1.12	0.72-1.75	.620	1.39	0.78-2.48	.270	0.92	0.46-1.83	.817
Dose: ≥54 vs <54 Gy	284/67	0.47	0.31-0.70	<.001	0.43	0.28-0.67	<.001	0.37	0.21-0.67	.001	0.40	0.21-0.75	.004
IDH mutation: yes vs no	240/58	0.63	0.40-0.99	.044	0.73	0.44-1.21	.220	0.85	0.45-1.61	.622	0.88	0.44-1.79	.718
1p/19q codeletion: yes vs no	79/117	0.35	0.20-0.62	<.001	0.33	0.17-0.64	.001	0.40	0.18-0.87	.021	0.31	0.15-0.64	.002

Abbreviations: A, astrocytoma and oligoastrocytoma (which was eliminated in the 2016 World Health Organization classification); CI, confidence interval; HR, hazard ratio; O, oligodendroglioma; OS, overall survival; PFS, progression-free survival.

DISCUSSION

With the RT dose as a continuous variable, to the best of our knowledge, this study is the first to quantify a dose-response relationship in patients with LGGs on the basis of modern technology. In our study, a dose-response was observed, and high-dose RT (≥54 Gy) was associated with improved survival. Multivariate analysis and split-sample validation showed that high-dose RT had a protective effect on OS and PFS. Importantly, our study demonstrated that high-dose RT might provide more benefit to patients with an *IDH* mutation/noncodeletion or *IDH* wild type than patients with an *IDH* mutation/codeletion. This is also the first report on the relationship between RT dose and molecular subgroups.

In patients with adult glioblastomas (WHO grade 4), a dose-effect relationship has been established, and 60 Gy is suitable.[9,10] However, in LGGs, the dose-response and the optimal dose are still disputed. It is challenging to conduct studies on the dose for LGGs because of the requirements for long-term follow-up. Different studies on RT dose have reported different or even contrary conclusions regarding tumor heterogeneity and treatment strategy. Earlier retrospective studies have observed a dose-response relationship in LGGs.[13-16] Although these studies were retrospective and had limited sample sizes, they found that patients who received high-dose RT (>52, >53, or even >55 Gy) had a potential benefit in comparison with those who received low-dose RT (<52, <53, or even <55 Gy). However, 2 randomized trials did not observe the dose-response. The European Organisation for Research and Treatment of Cancer (EORTC) 22844 trial (activated in 1985) and the North Central Cancer Treatment Group (NCCTG) 86-72-51 trial (activated in 1986) did not show an OS or PFS benefit from high-dose RT (59.4 and 64.8 Gy) over low-dose RT (45 and 50.4 Gy).[11,12] Even though these data are controversial, the conclusion from the aforementioned data indicates a suitable range of 52 to 59.4 Gy for LGGs. The data from our review of patients mirror this result. In our study, the 5-year survival rates of patients receiving doses of <50, 50 to 54, 55 to 59, and ≥59.4 Gy were 58.1%, 72.7%, 86.2%, and 80.8%, respectively (Supporting Fig. 3). The data indicated that the range of 54 to 59.4 Gy might be the optimal range for patients with LGGs. At present, a dose of 54 Gy is extensively used in clinical decisions and trials of LGGs. Although the final report in 2020 from Intergroup NCCTG 86-72-51 still showed no survival benefit with high-dose RT,[1] these studies (including EORTC 22844) were conducted early, before the year 1990, and they had many limitations in both

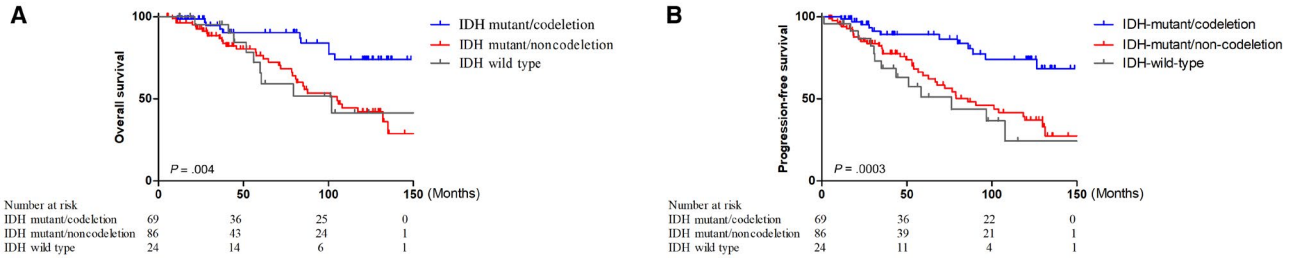

Figure 3. Molecular subgroup prognostic survival analyses. Three molecularly defined subgroups (*IDH* mutation/1p/19q codeletion, *IDH* mutation/1p/19q noncodeletion, and *IDH* wild type) were significantly associated with both (A) overall survival and (B) progression-free survival.

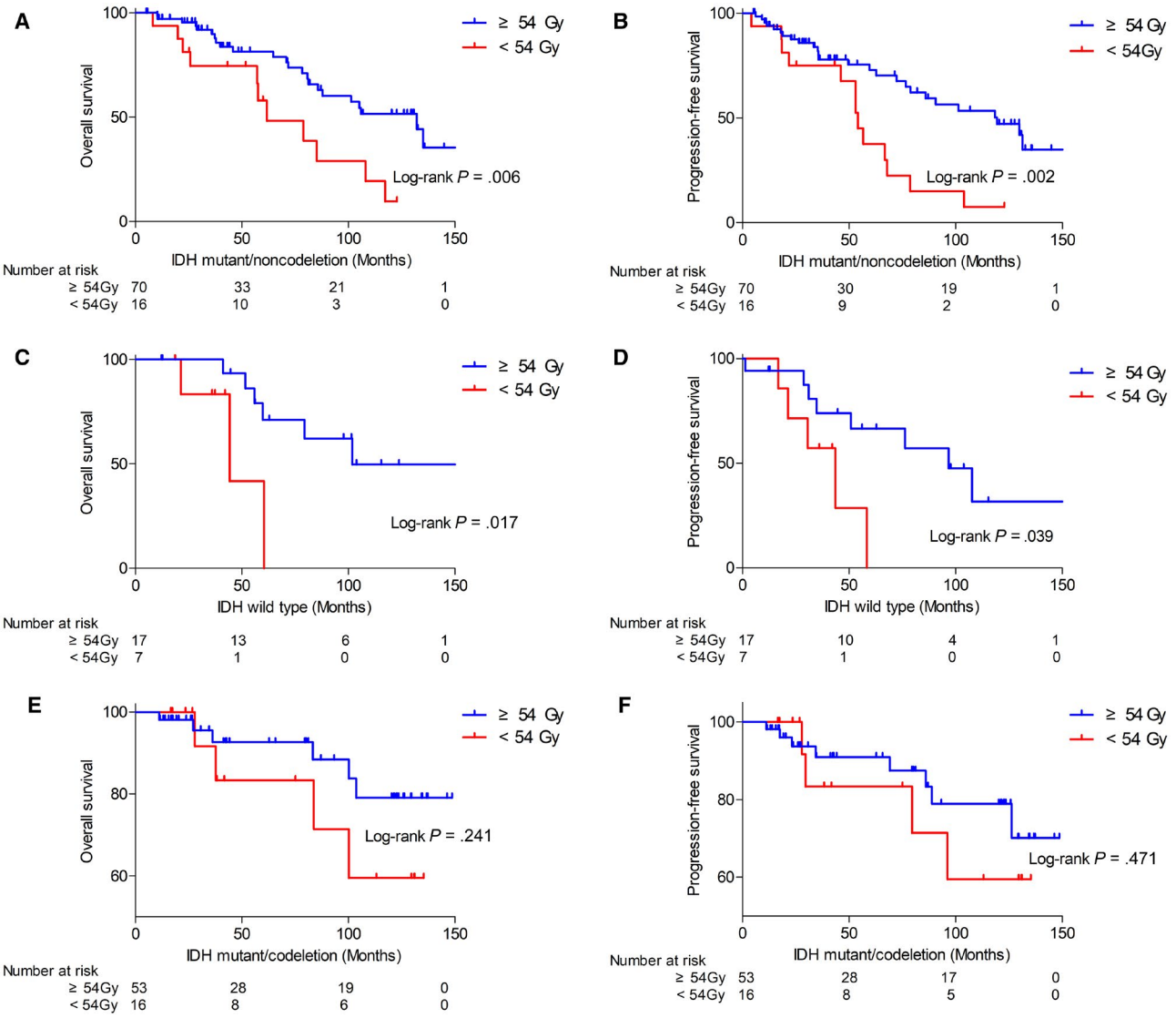

Figure 4. RT dose effects on the *IDH* mutation and 1p/19q status defined subgroups. Patients with (A,B) an *IDH* mutation/1p/19q noncodeletion or (C,D) *IDH* wild type could benefit from high-dose RT; (E,F) patients with an *IDH* mutation/1p/19q codeletion did not benefit from high-dose RT. RT indicates radiotherapy.

diagnostic and treatment modalities. Patients were treated in an era with older surgical and radiation techniques; CT was the main method for detecting tumor progression. There were also limitations in pathological diagnosis. Currently, IMRT, MRI, and especially molecular pathology are routinely used in clinical practice, and this has led to significant improvements in diagnosis and treatment. Therefore, additional clinical studies of RT dose are needed for reconsideration with modern technology.

LGGs display highly variable survival depending on the molecular subgroups. Therefore, prognostic estimates should be evaluated in the context of molecular characteristics. For the first time, we explored the dose-response in different molecular subgroups. According to the RTOG 9802 trial of LGGs, patients with *IDH* wild type belong to the poorest subgroup and see no clinical benefit from the addition of chemotherapy.[20] In our study, patients with *IDH* wild type showed improved survival with high-dose RT. Similarly, high-dose RT might provide a benefit to patients with an *IDH* mutation/1p/19 noncodeletion. However, our data showed that patients with an *IDH* mutation/1p/19q codeletion did not benefit from high-dose RT. Therefore, dose escalation in these patients should be performed with caution in light of the increasingly possible toxicities.

This study combined data from multiple institutions, and this provided advantages and disadvantages. The major advantages were as follows: 1) RT dose was evaluated as a continuous variable, 2) modern RT technology (3-dimensional conformal radiotherapy and IMRT) was used in this study, and 3) associations of molecular characteristics with RT dose were first reported. However, the limitations of our retrospective study should be acknowledged. First, although the result was demonstrated by IPTW-adjusted analysis using prematching cohorts, it is important to consider whether the current retrospective studies were biased with respect to the allocation of patients. In this study, although chemotherapy was not an independently prognostic factor and the benefits from high-dose RT were observed in both patients receiving and not receiving chemotherapy (Supporting Fig. 4), the results should be reproducible in prospective trials. Second, no information on quality of life was available. Theoretically, an increased RT dose results in reduced quality of life. Patients with LGGs who received RT showed a progressive decline in attentional functions in comparison with those who did not receive RT.[23] However, the final report from the NCCTG 86-72-51 trial showed that long-term cognitive function did not different significantly between patients who received 50.4 Gy and those who received 64.8 Gy.[1] The fractional dose in our study was 1.8 to 2.0 Gy. Published data show that the fractional dose of ≤2 Gy might minimize these side effects.[23,24] Third, the effect of the RT field on survival outcomes was not evaluated because of nonuniform data collection of target delineation from participating institutions. It is still controversial whether increasing the radiation therapy volume has a negative impact on survival or health-related quality of life.[25] Finally, *IDH* wild-type diffuse astrocytomas are not considered to be low-grade gliomas and, if these have *EGFR* amplification, +7/–10, or a *TERT* promoter mutation, are designated as *IDH* wild-type diffuse astrocytoma with molecular features of glioblastoma (WHO grade 4 according to the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy– Not Official WHO [cIMPACT NOW] update 3).[26] Unfortunately, the 3 molecular features were unable to be obtained in this retrospective study because of limited tissue availability. However, we analyzed the relationship between RT dose and survival on the basis of 240 patients with the *IDH* mutation. The results showed that patients with *IDH*-mutant LGGs could benefit from high-dose RT (Supporting Fig. 5). In addition, the curves for the *IDH* wild type and the *IDH* mutation/1p/19q noncodeletion are close to each other in our study, and this is not consistent with RTOG 9802.[20] However, high-risk patients who were older than 40 years or had undergone subtotal tumor resection were enrolled in RTOG 9802, whereas our cohort included low-risk LGGs (60 of 179 [33.5%]). We analyzed survival for high-risk patients (age ≥ 40 years or subtotal resection; 119 of 179 [66.5%]) and found that the *IDH* wild-type and *IDH*-mutation/1p/19q noncodeletion curves gradually separated (Supporting Fig. 6). The long-term survival for these patients, especially low-risk patients, requires longer follow-up, and this might be a weakness of our study. The low-risk or *IDH*-mutant/codeleted patients with the best outcomes need to be reassessed in future clinical trials to prevent excessive treatment.

In conclusion, clinicians and patients should be aware of the essential role of high-dose RT in LGGs. The RT dose-response was observed in patients with LGGs, and high-dose RT (≥54 Gy) was associated with improved survival. *IDH*-mutation/1p/19q noncodeletion or *IDH* wild-type patients may have improved survival with the administration of high-dose RT. Despite the many limitations of this retrospective study, our findings will help to define the standard of care and assist with decision-making as well as the design of prospective clinical trials for LGGs.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Yanwei Liu: Study concept and design, drafting of the manuscript, and patient follow-up. **Shuai Liu:** Study concept and design and drafting of the manuscript. **Guanzhang Li:** Statistical analysis. **Yanong Li:** Patient follow-up. **Li Chen:** Radiotherapy data collection. **Jin Feng:** Radiotherapy data collection. **Yong Yang:** Statistical analysis. **Tao Jiang:** Study concept, design, and coordination. **Xiaoguang Qiu:** Study concept, design, and coordination.

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