Original Article

Is Less More? Comparing Chemotherapy Alone With Chemotherapy and Radiation for High-Risk Grade 2 Glioma: An Analysis of the National Cancer Data Base

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BACKGROUND: The addition of chemotherapy to adjuvant radiotherapy (chemotherapy and radiation therapy [CRT]) improves overall survival (OS) for patients with high-risk grade 2 gliomas; however, the impact of chemotherapy alone (CA) is unknown. This study compares the OS of patients with high-risk grade 2 gliomas treated with CA versus CRT. **METHODS:** Patients with high-risk grade 2 gliomas (subtotal resection or age ≥ 40 years) with oligodendrogliomas, astrocytomas, or mixed tumors were identified with the National Cancer Data Base. Patients were grouped into CA and CRT cohorts. Univariate analyses and multivariate analyses (MVAs) were performed. Propensity score (PS) matching was also implemented. The Kaplan-Meier method was used to analyze OS. **RESULTS:** A total of 1054 patients with high-risk grade 2 gliomas were identified: 496 (47.1%) received CA, and 558 (52.9%) received CRT. Patients treated with CA were more likely (all *P* values < .05) to have oligodendroglioma histology (65.5% vs 34.2%), exhibit a 1p/19q codeletion (22.8% vs 7.5%), be younger (median age, 47.0 vs 48.0 years), and receive treatment at an academic facility (65.2% vs 50.3%). The treatment type was not a significant predictor for OS (*P* = .125) according to the MVA; a tumor size > 6 cm, astrocytoma histology, and older age were predictors for worse OS (all *P* values < .05). After 1:1 PS matching (n = 331 for each cohort), no OS difference was seen (*P* = .696) between the CA and CRT cohorts at 5 (69.3% vs 67.4%) and 8 years (52.8% vs 56.7%). **CONCLUSIONS:** No long-term OS difference was seen in patients with high-risk grade 2 gliomas treated with CA versus CRT. These findings are hypothesis-generating, and prospective clinical trials comparing these treatment paradigms are warranted. ***Cancer*** **2018;124:1169-78.**

KEYWORDS: chemotherapy, grade 2 glioma, low-grade glioma, National Cancer Data Base (NCDB), overall survival, radiotherapy.

INTRODUCTION

Low-grade gliomas (LGGs) are indolent primary brain tumors that are diffusely infiltrative, and they predominantly affect young adults. LGGs include both World Health Organization (WHO) grade 1 and grade 2 tumors, with the latter further risk-stratified into low- and high-risk tumors. Low-risk patients are defined as patients younger than 40 years old who undergo a gross total resection and can typically be managed with observation after surgery with a 5-year overall survival (OS) rate of 93%.[1] In contrast, high-risk patients (age ≥ 40 years, regardless of resection, or age < 40 years with subtotal resection/biopsy) demonstrate worse progression-free survival (PFS) and OS.[2] The Radiation Therapy Oncology Group (RTOG) 9802 study showed that for high-risk LGG patients, the addition of sequential procarbazine, lomustine, and vincristine (PCV) chemotherapy to radiotherapy (RT) dramatically improved median OS (13.3 vs 7.8 years; *P* = .003).[2] Because of the magnitude of this increase in OS, the current standard of care for high-risk grade 2 gliomas is adjuvant sequential chemotherapy and radiation.

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Although RTOG 9802 confirmed that the addition of chemotherapy improves OS, the role of chemotherapy alone (CA) in comparison with chemotherapy and radiation therapy (CRT) remains unclear. Single-arm, phase 2 clinical trials for patients with grade 2 glioma have demonstrated that temozolomide (TMZ) chemotherapy does have intracranial activity.[3,4] More recently, the phase 3 European Organization for Research and Treatment of Cancer 22033-26033 study[5] also investigated the efficacy of TMZ alone against RT alone. With a primary endpoint of PFS, the authors found no difference in outcome with RT alone versus TMZ alone. At the same time, the use of RT in the immediate postoperative period is associated with symptomatic improvement and prolonged PFS in comparison with delayed use of RT.[6] However, delaying the administration of RT until there is clinical progression is a management strategy that is frequently used because of concerns about the long-term toxicity associated with RT. With that in mind, clinicians often omit upfront RT, particularly for 1p19q-codeleted oligodendrogliomas, because they are reported to be inherently more sensitive to chemotherapy than other LGGs.[3,7-9] With no study to date comparing the treatment outcomes of CA and CRT, the current study was designed to compare the efficacy of CA and CRT for patients with high-risk grade 2 gliomas in the National Cancer Data Base (NCDB), a retrospective cancer registry that captures approximately 70% of newly diagnosed cancer cases in the United States and potentially provides large statistical power for evaluating OS.

MATERIALS AND METHODS

Patient Selection

The NCDB is maintained jointly by the American College of Surgeons and the American Cancer Society and includes patient information from more than 1500 Commission on Cancer–approved hospitals in the United States. The 2014 NCDB brain/central nervous system participant user file was used to select patients for this study. This file includes detailed patient information, including demographics, socioeconomic factors, disease and treatment characteristics, and OS. Review by the institutional review board was not required as this research study utilized the National Cancer Data Base (NCDB) which is a multi-institutional, de-identified cancer registry. Informed consent is also not applicable.

The NCDB participant user file was queried for patients diagnosed with WHO grade 2 gliomas from 2004 to 2013. For this analysis, patients were included only if they met the RTOG definition of high risk: age $\geq$ 40 years, regardless of the extent of resection, or age $<$ 40 years with subtotal resection or biopsy.[10] Patients with in situ disease, without a histologic confirmation of malignancy, or a brainstem location were all excluded, and this resulted in a total of 12,932 cases. We further excluded patients who did not receive chemotherapy. We then defined 2 groups: patients who received CRT and patients who received CA. For both groups, we excluded cases with missing outcomes and patients with delayed treatment (defined as the treatment started more than 6 months after the diagnosis). For the CRT arm, we excluded patients with inappropriate RT doses ($<$45 or $>$ 60 Gy), volumes (ie, dose not delivered to the brain), or modalities (ie, linear accelerator and Gamma Knife–based radiosurgery, brachytherapy, cobalt, electrons, strontium, and radioisotopes). The Consolidated Standards of Reporting Trials diagram for patient selection is shown in Figure 1.

Patient Demographics

The patient's age at diagnosis, sex, race, insurance status, education, median income quartile, and location (metropolitan vs rural) as well as the geographic location of the treatment facility and the treatment facility type were examined. The treatment facility was categorized as an academic/research center, which included National Cancer Institute–designated comprehensive cancer centers, or a nonacademic program, which included community cancer programs ($>$100 but $\leq$ 500 new annual cancer cases) and comprehensive community cancer programs ($>$500 new annual cancer cases). The geographic location was determined from the zip code of the patient recorded at the time of diagnosis. This was classified and compared as metropolitan versus urban/rural, as defined by the United States Department of Agriculture Economic Research Service (https://www.ers.usda.gov/data-products/rural-urban-continuum-codes). The Charlson-Deyo score was used as a surrogate marker for patient comorbidities. The Charlson-Deyo score was categorized as 0, 1, or 2 and higher to indicate increasing levels of comorbid conditions.[11]

Disease Characteristics

The following tumor-related variables were evaluated: year of diagnosis, primary site (eg, frontal lobe or cerebellum), laterality, pattern (unifocal vs multifocal), tumor size ($>$6 vs $<$ 6 cm), WHO grade 2 only, histology (oligodendroglial, astrocytic, or mixed), chromosome 1p loss of

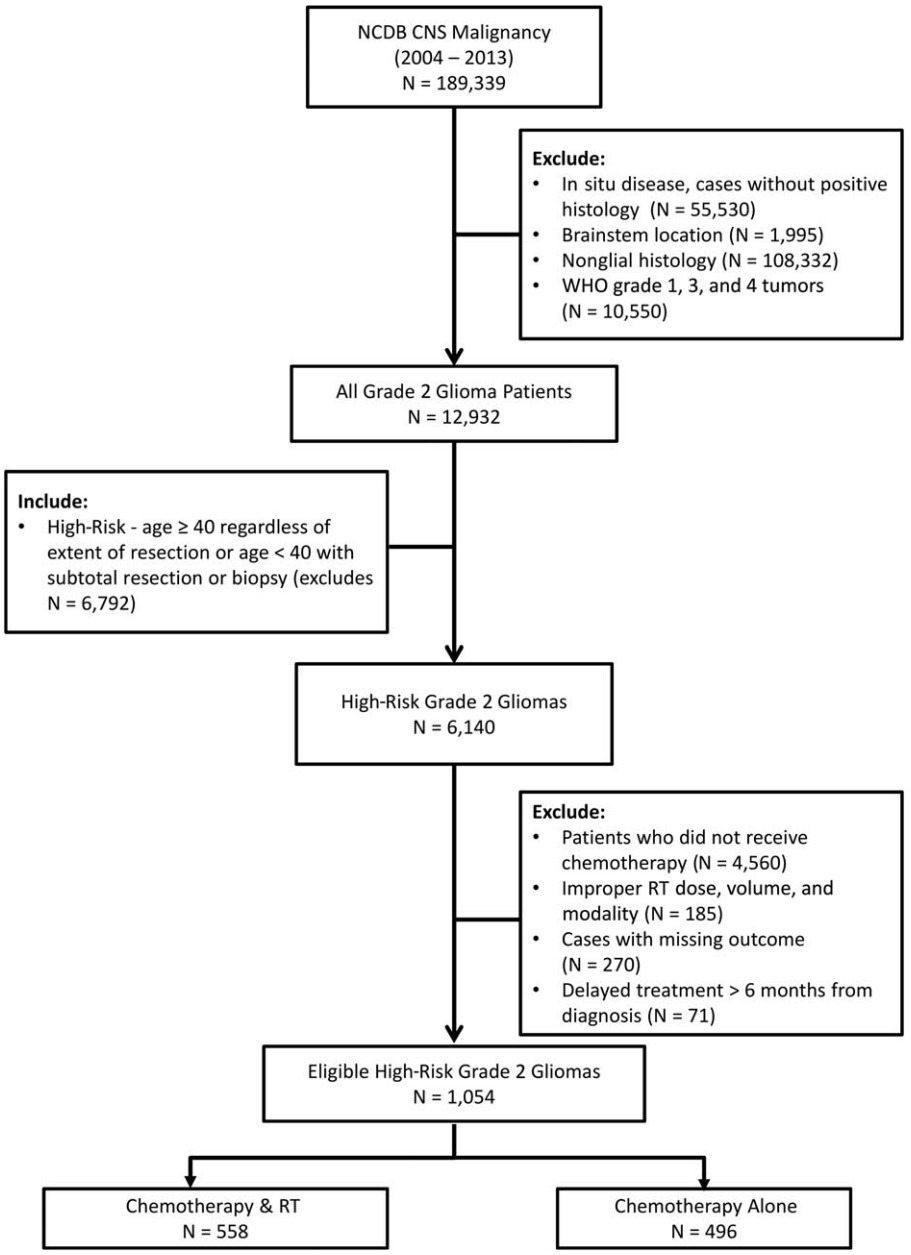


Figure 1. Consolidated Standards of Reporting Trials diagram for all patients. CNS indicates central nervous system; NCDB, National Cancer Data Base; RT, radiotherapy; WHO, World Health Organization.

heterozygosity (LOH), chromosome 19q LOH, and extent of surgical resection.

Treatment Characteristics

The times to surgery and the initiation of adjuvant therapy were noted. All patients in the study received chemotherapy. Patients with a delayed start of adjuvant treatment > 6 months were excluded. The sequencing of CRT was evaluated: chemotherapy followed by RT, RT followed by chemotherapy, and concurrent CRT (defined as either modality starting within 2 weeks of the other). The use of single-agent chemotherapy versus multi-agent chemotherapy was also examined. The total RT dose delivered was also taken into account.

Statistical Analysis

The statistical analysis was conducted with SAS 9.4 (SAS, Cary, North Carolina). The univariate association

TABLE 1. Baseline Patient Characteristics Stratified by Treatment Type

Variable	Cohorts		*P*
	Chemotherapy Alone (n = 496)	Chemotherapy Plus Radiation (n = 558)	
Age, No. (%)			
<40 y	85 (17.14)	75 (13.44)	.095
≥40 y	411 (82.86)	483 (86.56)	
Age			
No.	496	558	**.015**
Mean, y	47.61	49.32	
Median, y	47	48	
Minimum, y	18	19	
Maximum, y	82	88	
SD, y	11.1	11.56	
Sex, No. (%)			
Male	272 (54.84)	311 (55.73)	.770
Female	224 (45.16)	247 (44.27)	
Race, No. (%)			
White	451 (90.93)	521 (93.37)	.140
Other	45 (9.07)	37 (6.63)	
No high school degree, No. (%)			
≥29%	56 (11.81)	61 (11.55)	.417
20%-28.9%	97 (20.46)	117 (22.16)	
14%-19.9%	108 (22.78)	138 (26.14)	
<14%	213 (44.94)	212 (40.15)	
Median income quartiles, No. (%)			
<$30,000	50 (10.55)	45 (8.51)	.311
$30,000-$35,999	70 (14.77)	76 (14.37)	
$36,000-$45,999	116 (24.47)	155 (29.3)	
≥$46,000	238 (50.21)	253 (47.83)	
Facility type, No. (%)			
Non-academic program	143 (34.79)	240 (49.69)	**<.001**
Academic/research program	268 (65.21)	243 (50.31)	
Geographic location, No. (%)			
Metro	387 (82.34)	428 (81.06)	.602
Urban/rural	83 (17.66)	100 (18.94)	
Charlson-Deyo score, No. (%)			
0	420 (84.68)	457 (81.9)	.229
≥1	76 (15.32)	101 (18.1)	
Year of diagnosis, No. (%)			
2004-2005	63 (12.7)	60 (10.75)	.602
2006-2007	73 (14.72)	99 (17.74)	
2008-2009	86 (17.34)	102 (18.28)	
2010-2011	147 (29.64)	163 (29.21)	
2012-2013	127 (25.6)	134 (24.01)	
Histology, No. (%)			
Mixed glioma	93 (18.75)	132 (23.66)	**<.001**
Astrocytoma	78 (15.73)	235 (42.11)	
Oligodendroglioma	325 (65.52)	191 (34.23)	
Tumor size, No. (%)			
≤6 cm	208 (41.94)	261 (46.77)	.127
>6 cm	81 (16.33)	98 (17.56)	
Unknown	207 (41.73)	199 (35.66)	
Radiotherapy dose, No. (%)			
45-50.4 Gy	0	88 (15.77)	.127
50.41-54 Gy	0	244 (43.73)	
54.01-60 Gy	0	226 (40.5)	
Codeletion of 1p19q, No. (%)			
Both positive	113 (22.78)	42 (7.53)	**<.001**
Either negative	41 (8.27)	58 (10.39)	
Unknown	342 (68.95)	458 (82.08)	
Unifocal vs multifocal tumor, No. (%)			
Unifocal	249 (50.2)	243 (43.55)	.093
Multifocal	12 (2.42)	17 (3.05)	
Unknown	235 (47.38)	298 (53.41)	

TABLE 1. *Continued*

Variable	Cohorts: Chemotherapy Alone (n = 496)	Cohorts: Chemotherapy Plus Radiation (n = 558)	*P*
Surgical resection, No. (%)			
Biopsy	78 (15.92)	95 (17.21)	.258
Subtotal resection	144 (29.39)	133 (24.09)	
Gross total resection	51 (10.41)	56 (10.14)	
Other/unknown	217 (44.29)	268 (48.55)	
Chemotherapy, No. (%)			
Chemotherapy administered (number and type of agents unknown)	37 (7.46)	22 (3.94)	.045
Single agent	443 (89.31)	516 (92.47)	
Multiple agents	16 (3.23)	20 (3.58)	
Time to start of adjuvant therapy, No. (%)			
<2.5 mo	348 (70.16)	454 (81.36)	**<.001**
≥2.5 mo	148 (29.84)	104 (18.64)	
Tumor size, cm			.875
Mean	5.57	5.47	
Median	4.8	4.8	
Follow-up time, mo			.531
Mean	54.21	52.78	
Median	47.39	48.24	

Abbreviation: SD, standard deviation.
Bolded values are significant.

between each variable and the study cohorts (CRT vs CA) was assessed with a chi-square test for categorical covariates and with an analysis of variance for numerical covariates. The univariate associations between each covariate and the study cohorts as well as the study outcome of OS were assessed with Cox proportional hazards models and log-rank tests. A multivariate Cox proportional hazards model was fit with a backward variable selection method and with the application of $\alpha = .20$ removal criteria. The stratified analysis was conducted by the inclusion of the interaction term between the study arms and a stratified variable (eg, histology, extent of resection, or codeletion of 1p19q) in a multivariate model, and then, hazard ratios (HRs) along with 95% confidence intervals (CIs) were estimated for the study cohorts for each level of the stratified variable. Kaplan-Meier plots were generated to compare the survival stratified by the treatment type along with the log-rank *P* value.

The propensity score (PS) matching method was also implemented to minimize selection bias. A logistic regression model for CRT versus CA was performed to estimate the PS for all covariates that predicted for OS. Patients from each study cohort were matched to each other in a 1:1 ratio according to the PS with a greedy 5-1 digit match algorithm.[12] After the matching, the covariate balance between the 2 cohorts was evaluated with the standardized differences, and a value < 0.1 was considered a negligible imbalance.[13] The effect of the treatment group was then estimated in the matched sample with a Cox model with a robust variance estimator for OS.[14] OS was defined as the months from the date of adjuvant therapy to the date of death or last follow-up.

RESULTS

Patient Characteristics

A total of 1054 patients met our study criteria: 558 (53%) were in the CRT arm and 496 (47%) were in the CA arm. The median follow-up time for all patients was 55.1 months. Table 1 lists the baseline patient characteristics stratified by the treatment type. An unadjusted univariate analysis (UVA) showed that patients receiving CA were more likely to be younger (median age, 47 vs 48 years; $P = .015$), to be treated at an academic/research program (65.2% vs 50.3%; $P < .001$), to have oligodendroglial histology (65.5% vs 34.2%; $P < .001$), to have a codeletion of 1p19q (22.8% vs 7.5%; $P < .001$), and to have a longer mean duration to the start of adjuvant therapy (2.04 vs 1.77 months; $P < .001$). The median radiation dose delivered was 54.0 Gy for patients in the CRT arm, and the median time to the start of adjuvant therapy was 1.54 months for all patients. For chemotherapy, 91% of the patients received single-agent chemotherapy, whereas 3.4% received multi-agent chemotherapy, and 5.6% of

TABLE 2. Multivariate Analysis for Overall Survival

Covariate	No.	Hazard Ratio (95% CI)	*P*
Cohort			
Chemotherapy plus radiation	558	1.21 (0.95-1.54)	.125
Chemotherapy alone	496	—	—
Sex			
Male	583	1.18 (0.94-1.48)	.152
Female	471	—	—
Tumor size			
Unknown	406	1.74 (1.36-2.23)	**<.001**
>6 cm	179	1.51 (1.08-2.11)	**.015**
≤6 cm	469	—	—
Charlson-Deyo score			
≥1	177	1.29 (0.97-1.72)	.077
0	877	—	—
Histology			
Mixed glioma	225	1.42 (1.03-1.95)	**.032**
Astrocytoma	313	3.12 (2.39-4.07)	**<.001**
Oligodendroglioma	516	—	—
Age			
≥40 y	894	2.03 (1.32-3.13)	**.001**
<40 y	160	—	—
Time to start of adjuvant therapy (from diagnosis)			
<2.5 mo	802	1.52 (1.11-2.07)	**.009**
≥2.5 mo	252	—	—

Abbreviation: CI, confidence interval.
Bolded values are significant.

the patients had unknown chemotherapy types and agents.

OS

According to the UVA for OS, the receipt of CRT versus CA predicted worse OS (HR, 1.64; 95% CI, 1.30-2.06; $P < .001$; Supporting Fig. 1 [see online supporting information]). This effect persisted regardless of the sequencing of RT (concurrent administration, chemotherapy following RT, or RT followed by chemotherapy; Supporting Fig. 2 [see online supporting information]).

Other variables found to be significant predictors for survival in the UVA included the following: age ≥ 40 years (HR, 1.92; 95% CI, 1.25-2.94; $P = .003$), astrocytoma histology (HR, 3.30; 95% CI, 2.57-4.25; $P < .001$), mixed histology glioma (HR, 1.41; 95% CI, 1.03-1.94; $P = .032$), unknown (HR, 2.59; 95% CI, 1.53-4.37; $P < .001$) or negative 1p19q codeletion status (HR, 2.44; 95% CI, 1.26-4.69; $P = .008$), RT dose (HR, 1.07; 95% CI, 1.02-1.11; $P = .004$), and shorter time to the start of adjuvant therapy from the diagnosis (<2.5 months; HR, 1.75; 95% CI, 1.28-2.37; $P < .001$; Supporting Table 1 [see online supporting information]).

The multivariate analysis (MVA) for OS revealed that the receipt of RT was no longer a statistically significant predictor for OS (Table 2). However, tumor size > 6.0 cm (HR, 1.51; 95% CI, 1.08-2.11; $P = .015$) and an unknown tumor size (HR, 1.74; 95% CI, 1.36-2.23; $P < .001$) continued to be predictors for worse survival in comparison with a tumor size ≤ 6.0 cm. Because unknown tumor size could be a potential confounding variable, MVA for the effect of CA versus CRT was also performed with stratification for tumor size groups (Supporting Table 2 [see online supporting information]); this revealed that the treatment type was still not a factor for OS (type-3 $P = .473$).

Histology was also a predictor for OS in MVA: astrocytoma (HR, 3.12; 95% CI, 2.39-4.07; $P < .001$) and mixed histology glioma (HR, 1.42; 95% CI, 1.03-1.95; $P = .032$) both conferred an increased risk of death in comparison with oligodendroglioma histology. After stratification for the tumor histology type, MVA again revealed that the treatment type was not a predictor for OS (type-3 P value = .270). An age ≥ 40 years (HR, 2.03; 95% CI, 1.32-3.13; $P = .001$) and a shorter duration to the start of adjuvant therapy (<2.5 months; HR, 1.52; 95% CI, 1.11-2.07; $P = .009$) were also predictors for worse OS.

PS Analysis

After 1:1 PS matching, the baseline patient demographics and tumor and treatment characteristics were found to be similar (ie, standardized difference < 0.10; Table 3). A total of 331 patients from the CRT group were balanced

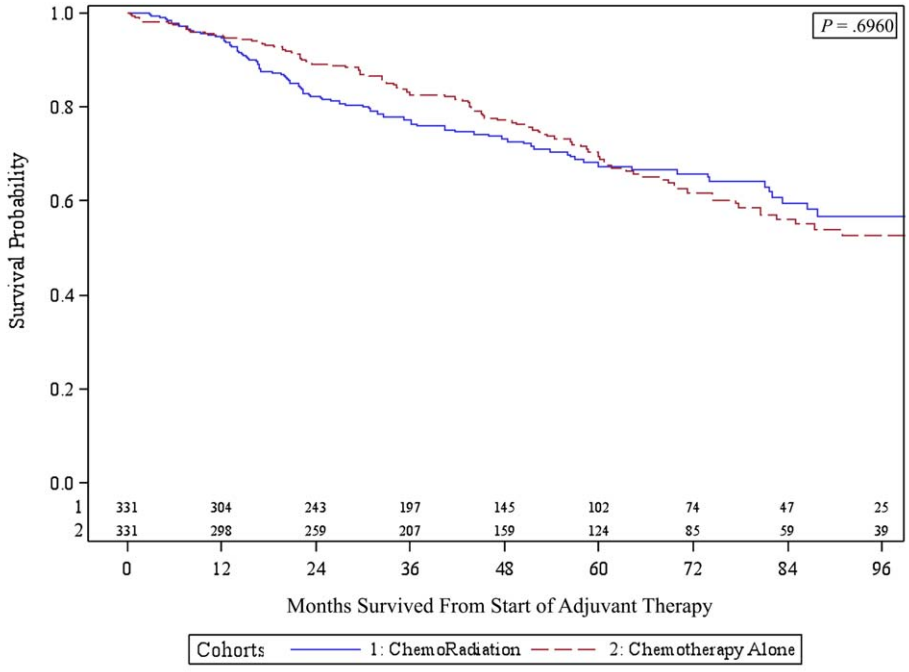
TABLE 3. Propensity Score Matching Showing Standardized Differences < 0.1 Between the 2 Groups for All Variables Affecting Survival

Covariate	Cohorts		Parametric *P*	Standardized Difference
	Chemotherapy Alone (n = 331)	Chemotherapy Plus Radiation (n = 331)		
Sex				
Male	181 (54.68)	185 (55.89)	.755	0.024
Female	150 (45.32)	146 (44.11)		0.024
Tumor size				
≤6 cm	143 (43.2)	142 (42.9)	.958	0.006
>6 cm	66 (19.94)	69 (20.85)		0.022
Unknown	122 (36.86)	120 (36.25)		0.013
Charlson-Deyo score				
0	278 (83.99)	281 (84.89)	.748	0.025
≥1	53 (16.01)	50 (15.11)		0.025
Age				
<40 y	51 (15.41)	46 (13.9)	.583	0.043
≥40 y	280 (84.59)	285 (86.1)		0.043
Time to start of adjuvant therapy				
<2.5 mo	255 (77.04)	251 (75.83)	.714	0.028
≥2.5 mo	76 (22.96)	80 (24.17)		0.028
Histology				
Mixed glioma	74 (22.36)	78 (23.56)	.931	0.029
Astrocytoma	74 (22.36)	72 (21.75)		0.015
Oligodendroglioma	183 (55.29)	181 (54.68)		0.012
Codeletion of 1p19q				
Both positive	42 (12.69)	41 (12.39)	.955	0.009
Either negative	33 (9.97)	31 (9.37)		0.020
Unknown	256 (77.34)	259 (78.25)		0.022
Unifocal vs multifocal tumor				
Unifocal	140 (42.3)	142 (42.9)	.841	0.012
Multifocal	7 (2.11)	5 (1.51)		0.045
Unknown	184 (55.59)	184 (55.59)		0.000
Chemotherapy				
Chemotherapy administered (number and type of agents unknown)	13 (3.93)	15 (4.53)	.904	0.030
Single agent	307 (92.75)	304 (91.84)		0.034
Multiple agents	11 (3.32)	12 (3.63)		0.016
Surgical resection				
Biopsy	50 (15.34)	58 (17.63)	.464	0.062
Subtotal resection	77 (23.62)	65 (19.76)		0.094
Gross total resection	29 (8.9)	37 (11.25)		0.078
Other/unknown	170 (52.15)	169 (51.37)		0.016

for all known covariates against 331 patients from the CA group. The adjusted Kaplan-Meier survival curves stratified by treatment groups are shown in Figure 2. After PS balancing, the 5-year OS rates for CA (69.3%; 95% CI, 63.0%-74.8%) and CRT (67.4%; 95% CI, 61.2%-72.9%) and the 8-year OS rates for CA (52.8%; 95% CI, 44.8%-60.2%) and CRT (56.7%; 95% CI, 48.3%-64.2%) were not statistically different ($P = .696$). The effect of the treatment group was then further estimated in the matched sample with a Cox model with a robust variance estimator[14] for OS, which yielded an HR of 1.01 (95% CI, 0.81-1.36; $P = .696$) for CRT versus CA.

DISCUSSION

LGG is a disease entity that presents a unique challenge in terms of study and improving outcomes. Because it is relatively rare—only 2000 cases are diagnosed annually in the United States—developing phase 3 clinical trials requires large, multi-institutional, cooperative group efforts. Furthermore, with median survival rates as high as 13 years, clinical trials require decades to mature and report significant findings. Because the NCDB captures 70% of all diagnosed cancer cases in the United States and follows patients for up to 10 years in a multi-institutional setting, it offers a unique, potentially well-suited opportunity for



Cohorts	No. of Subjects	Event	Censored	Median Survival (95% CI)	12-mo Survival	60-mo Survival	84-mo Survival	96-mo Survival
Chemotherapy + Radiation	331	100 (30%)	231 (70%)	NA (87.9, NA)	94.7% (91.7%, 96.7%)	67.4% (61.2%, 72.9%)	59.6% (51.9%, 66.5%)	56.7% (48.3%, 64.2%)
Chemotherapy Alone	331	103 (31%)	228 (69%)	108.3 (80.6, NA)	95.4% (92.4%, 97.2%)	69.3% (63.0%, 74.8%)	56.1% (48.5%, 63.0%)	52.8% (44.8%, 60.2%)

Figure 2. Kaplan-Meier survival analysis of propensity score–matched patients stratified by treatment group. CI indicates confidence interval; NA, not available.

investigating questions about LGG that would otherwise require significant resources to answer.

To the best of our knowledge, this is the largest series of patients with high-risk LGG ever reported. Furthermore, we could not find any retrospective or prospective series comparing CA and CRT for patients with high-risk LGG; that makes this study the first ever published on this topic. We found that, even after rigorous statistical techniques were used to eliminate a selection bias, for patients with high-risk grade 2 gliomas, the addition of RT to chemotherapy, regardless of sequencing, did not lead to an improvement in 5- and 8-year OS.

The results of MVA for OS show that astrocytoma histology (HR, 3.12), an age $\geq$ 40 years (HR, 2.03), and mixed glioma (HR, 1.42) were all associated with worse OS ($P < .05$). These findings are consistent with multiple previously reported studies.[15-18] Moreover, a shorter time to the initiation of adjuvant therapy (<2.5 months) was also noted to be associated with worse OS (HR, 1.52; $P = .009$). This likely reflects the underlying clinical practice of early adjuvant therapy for patients with adverse pathologic features such as astrocytomas, neurologic symptoms necessitating early adjuvant therapy, and an older age, which have been previously reported to be unfavorable prognostic factors for survival.[18]

The outcome of our CRT arm is directly comparable to the outcome of the RT-PCV arm of RTOG 9802.[2] The 5-year OS rate for our PS-matched CRT cohort with 331 patients was 67%, whereas the 5-year survival rate was 72% for the 125 patients in the RT-PCV group of RTOG 9802 as published in the initial 2012 report.[10] Initially, our Kaplan-Meier curves remained separated in favor of the CA alone arm. However, at 5 years, the CRT curve crossed and surpassed the CA curve. On further follow-up, at 8 years, 57% of the patients were alive in the CRT arm of our study, whereas approximately 65% of the patients were alive in the RT-PCV arm of RTOG 9802. This difference in survival is larger than expected because our matched CRT cohort had a higher fraction with oligodendroglioma histology

(53.5% were oligodendroglial tumors, 22% were astrocytic tumors, and the remaining 24.5% were mixed, whereas the proportions in the RTOG 9802 RT-PCV arm were 40%, 29%, and 31%, respectively). The current study has key differences in comparison with RTOG 9802 that may have contributed to these dissimilar results at 8 years: the median follow-up in our analysis was 55.1 months (4.6 years), whereas the median follow-up in RTOG 9802 was 142.8 months (11.9 years). This is particularly important because in RTOG 9802, survival did not begin to differ between the groups until 4 years. With our median follow-up of approximately 4.6 years, this analysis may not be capturing the potentially delayed difference in OS between these groups. Furthermore, RTOG 9802 exclusively used PCV chemotherapy, a multi-agent regimen. In our analysis, the majority of the patients (91%) received single-agent chemotherapy. Even though multiple studies in patients with grade 3 gliomas suggest no difference in survival between standard forms of PCV and TMZ,[19,20] it remains unknown whether these 2 regimens have different efficacies for grade 2 gliomas.

For a more modern comparison, in the preliminary results of RTOG 0424,[21] which is a phase 2 trial that evaluated the efficacy of concurrent and adjuvant TMZ with RT for patients with high-risk grade 2 gliomas, the 5-year OS was reported to be 57.1%. Our outcomes are better than the preliminary outcomes of RTOG 0424 for 2 possible reasons. First, because of the nature of this trial, 55% of the patients in RTOG 0424 had astrocytic tumors, whereas 22% did in our group; second, the definition of high-risk patients in RTOG 0424 was 3 or more risk factors (age $\geq$ 40 years, astrocytoma histology, bihemispherical tumor, preoperative tumor diameter $\geq$ 6 cm, or preoperative neurological function status- $>$ 1). Unfortunately, we could not directly compare the outcomes of our CA cohort with those of the TMZ alone arm of the European Organization for Research and Treatment of Cancer 22033-26033 trial[5] because the primary endpoint and reported results of that study are in the form of PFS.

Despite the application of an extensive array of statistical tools, our study has a few limitations. The median follow-up time for all patients was 55.1 months, and this makes it difficult to provide long-term outcomes for an indolent diagnosis such as LGG. The isocitrate dehydrogenase mutation status was not available in the NCDB and hence was not included in our analysis. Because of the limited number of patients with codeleted tumors, a subgroup analysis of the impact of the treatment type on LOH of 1p/19q could not be performed. The type, dose, and duration of chemotherapy are not recorded in the NCDB; although 91% received a single-agent regimen, it is possible that these patients may have received another agent (eg, nitrosoureas). Furthermore, multiple variables had unknown results; they included the tumor size (37% unknown), codeletion status (78% unknown), and extent of surgical resection (53% unknown). All of these variables are known prognostic factors and likely contributed to the selection bias inherent in this retrospective study. The strengths of our analysis include the use of MVA and PS analysis to mitigate the effect of the selection bias. However, PS analysis cannot account for a selection bias for other variables that were not captured in the database, including neurologic symptoms.

RT has remained the treatment of choice for several decades and has served as the control arm in most randomized trials; however, since the introduction of the oral alkylating agent TMZ, physicians have been increasingly deferring RT until disease progression for select patients, despite incomplete evidence. In particular, patients with a 1p19q codeletion, because of their chemosensitivity,[7,8] are often selected for upfront chemotherapy followed by salvage RT at the time of progression. The results of our study suggest that CRT is not associated with statistically significant higher survival in comparison with CA. Because a selection bias exists toward favorable characteristics for CA patients, we believe the finding that CA and CRT may be similar is only hypothesis-generating. Further studies in the form of randomized clinical trials comparing these treatment paradigms are warranted. In the meantime, we recommend that the standard of care remain adjuvant CRT as demonstrated in RTOG 9802.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Jaymin Jhaveri: Conceptualization, methodology, visualization, writing–original draft, project administration, and writing–review and editing. **Yuan Liu**: Methodology, software, formal analysis, data curation, project administration, funding acquisition, and writing–review and editing. **Mudit Chowdhary**: Writing–original draft and writing–review and editing. **Zachary S. Buchwald**:

Writing–review and editing. **Theresa W. Gillespie**: Investigation, resources, project administration, funding acquisition, and writing–review and editing. **Jeffrey J. Olson**: Writing–review and editing. **Alfredo D. Voloschin**: Writing–review and editing. **Bree R. Eaton**: Writing–review and editing. **Hui-Kuo G. Shu**: Writing–review and editing. **Ian R. Crocker**: Writing–review and editing. **Walter J. Curran**: Supervision and writing–review and editing. **Kirtesh R. Patel**: Conceptualization, methodology, visualization, writing–original draft, supervision, project administration, and writing–review and editing.

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