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Scientific Article

The Association Between Radiation Therapy Dose and Overall Survival in Patients With Intracranial Infiltrative Low-Grade Glioma Treated With Concurrent and/or Adjuvant Chemotherapy

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Abstract

Purpose: Previous trials have shown no benefit for radiation therapy (RT) dose escalation when RT is given as adjuvant monotherapy for infiltrative low-grade glioma (LGG). However, the current standard of care for high-risk LGG is RT with concurrent and/or adjuvant chemotherapy. The effect of RT dose escalation on overall survival (OS) in the setting of concurrent and/or adjuvant chemotherapy is not well established.

Methods and Materials: We used the National Cancer Database to select records for adult patients with intracranial grade 2 LGG diagnosed between 2004 and 2015. Patients must have received adjuvant external beam RT with concurrent and/or adjuvant chemotherapy. RT dose level was categorized as standard (45-54 Gy) or high (>54-65 Gy). Multivariable and propensity score matched analyses were used.

Results: The study cohort consisted of 1043 patients, of whom 644 (62%) received standard dose (median, 54 Gy) and 399 (38%) received high-dose RT (median, 60 Gy). RT dose level was not associated with OS (hazard ratio, 1.2; $P = .1$) in multivariable analysis. Propensity score matching yielded 380 matched pairs (n = 760). There was no difference in OS for high-dose versus standard-dose RT in the matched cohort (5-year OS 64% vs 69%; $P = .14$) or in the 2 prespecified subgroups of astrocytoma histology and 1p/19q noncodeleted.

Conclusions: Adjuvant RT dose escalation above 54 Gy in the setting of concurrent and/or adjuvant chemotherapy was not associated with improved OS for patients with infiltrative LGG in this National Cancer Database retrospective study. This was also true for the subgroups with less chemotherapy-sensitive disease, including astrocytoma histology and 1p/19q noncodeleted, although these analyses were limited by small size. Methods to improve OS other than RT dose escalation in the setting of concurrent and/or adjuvant chemotherapy should be considered for patients with poor-prognosis LGG.

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Introduction

Infiltrative low-grade gliomas (LGGs) account for approximately 5% to 10% of all primary brain tumors in adults in the United States each year.[1] The standard of care for the treatment of LGG has significantly changed recently based on risk stratification for progression and the publication of several randomized trials. In the era before molecular classification, it was demonstrated that immediate postoperative radiation therapy (RT) alone to 54 Gy was associated with a progression-free survival (PFS), but not overall survival (OS), benefit compared with RT treatment at the time of progression.[2] Additionally, postoperative RT dose escalation (59.4 vs 45 Gy and 64.8 vs 50.4 Gy, respectively) given as adjuvant monotherapy was not associated with a benefit in either PFS or OS.[3,4]

The favorable prognostic risk factors identified from US trials were age <40 years and neurosurgeon-defined gross total resection (GTR). The Radiation Therapy Oncology Group (RTOG) 9802 trial used this risk stratification and demonstrated that patients with low-risk LGG (defined as age <40 years and GTR) who were observed postoperatively had a 5-year PFS of 48% and a 5-year OS of 93%.[5] This indicates there is a significant risk of progression without adjuvant therapy but that salvage treatment given at the time of progression successfully preserves survival. High-risk patients (defined as those who were not <40 years of age with a GTR) were randomized to postoperative RT to 54 Gy with or without 6 cycles of adjuvant procarbazine, lomustine, vincristine (PCV) chemotherapy.[6] Long-term outcomes demonstrated a significant OS benefit for RT + PCV compared with RT alone independent of histology or IDH1 mutation status. Because of the toxicity of PCV chemotherapy, RT with concurrent and/or adjuvant temozolomide (TMZ) has been adopted with demonstrated efficacy compared with historical controls of RT alone.[7] Additionally, it was recently shown that TMZ monotherapy had no benefit for PFS compared with RT alone in patients with high-risk LGG and may be associated with worse PFS within certain molecular subsets.[8] These data formed the basis for the consensus recommendation for adjuvant RT with concurrent and/or adjuvant chemotherapy as standard of care for patients with high-risk LGG.[9]

However, the role of RT dose escalation in the setting of concurrent and/or adjuvant chemotherapy is not known given that the previous negative trials of RT dose escalation were in the adjuvant RT monotherapy setting. The goal of this study was to determine whether there is an association between adjuvant RT dose and OS in the setting of concurrent and/or adjuvant chemotherapy for patients with LGG using the National Cancer Database (NCDB).

Methods and Materials

Data collection and cohort definition

The study was conducted using the NCDB, which is a national hospital-based cancer registry that includes nearly 70% of incident cancer cases in the United States.[10] This study was institutional review board exempt, and patient consent was not required due to the publicly available, deidentified nature of the NCDB.

We included adult patients (age ≥18 years) with grade 2 glioma (International Classification of Disease for Oncology, Third Edition [ICD-O-3] histology codes 9380, 9382, 9400, 9411, 9420, 9424, 9450, and 9451). World Health Organization tumor grade of 2 was defined based on the CS Site-Specific Factor 1 Brain variable value of 020. Tumor location was limited to intracranial as defined by ICD-0-3 topographical code C71.X, with brain stem location (C71.7) excluded. Other criteria were year of diagnosis 2004 to 2015 and no evidence of metastatic disease at diagnosis (CS_mets_at_dx value of 00, 10, or 99). We excluded patients who did not have known vital status or who died within 30 days of initial surgery. We additionally excluded patients who did not receive adjuvant RT, received adjuvant RT modalities other than external beam RT, had unknown RT dose delivered, received atypical RT dosing ("typical" defined as 45-65 Gy), or did not start RT within 6 months of surgery. Patients must have also received chemotherapy (single or multiagent) and chemotherapy must have started within 7 days before or 75 days after the initiation of RT (which is approximately 30 days after the completion of a 6-week course of RT). An additional 6 patients were excluded due to unknown median household income quartile based on ZIP code or unknown proportion of residents with no high school diploma based on ZIP code. This resulted in a cohort of 1043 patients (Fig 1).

Predictor variables

Variables included in the analysis included patient age, sex, race, insurance status, median household income based on ZIP code, proportion of residents with no high school diploma based on ZIP code, urban/rural category, distance from home ZIP code to facility, Charlson/Deyo comorbidity index, year of diagnosis, facility type, tumor size (≤5 cm vs >5 cm),[11] extent of resection (subtotal resection vs GTR), chemotherapy (single vs multiagent), tumor histology (astrocytoma, oligodendroglioma, mixed, or not otherwise specified), and loss of heterozygosity (LOH) of 1p and 19q.

Statistical analyses

Patients were grouped according to adjuvant RT dose. Standard dose was defined as 45 to 54 Gy and high dose

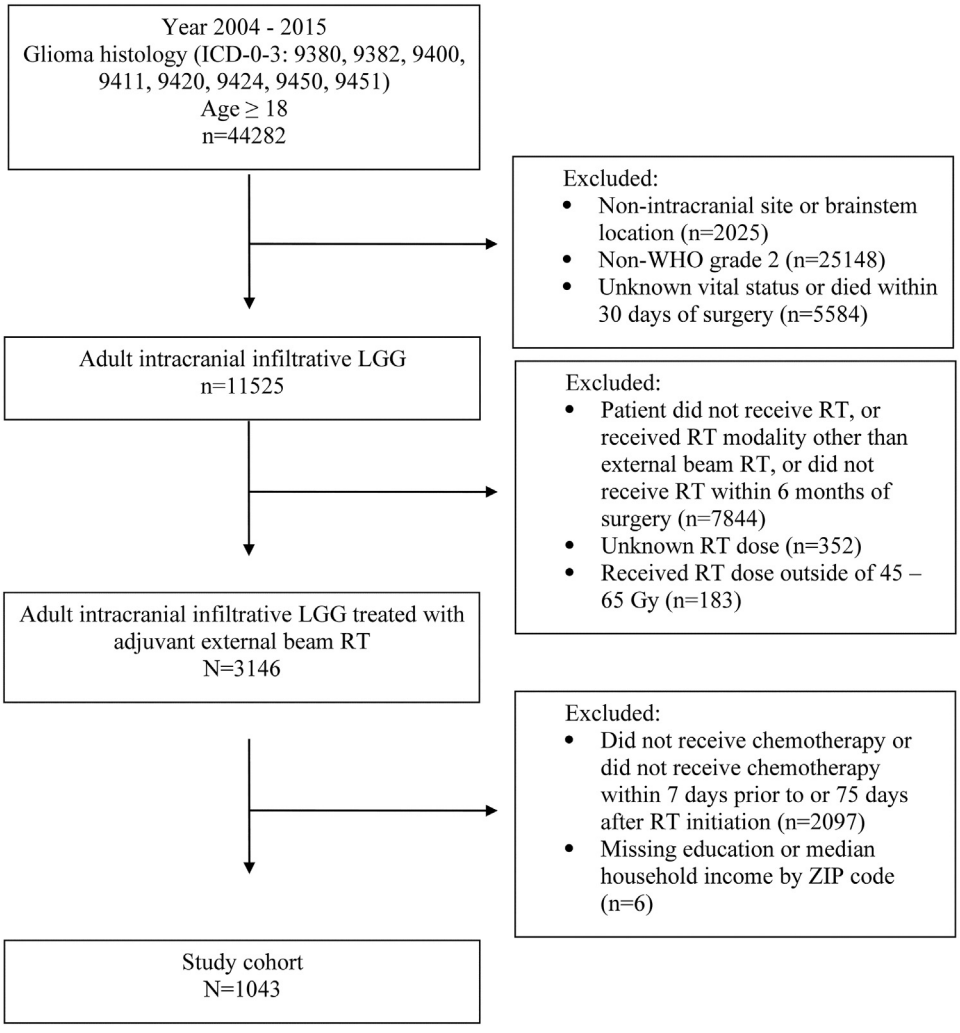

Figure 1 Patient selection flow chart. *Abbreviations:* LGG = low-grade glioma; RT = radiation therapy; WHO = World Health Organization.

was defined as >54 to 65 Gy. Continuous variables were reported as median with interquartile range (IQR), and categorical variables were reported as number and percentage. Variables were compared using the χ^2 test or Wilcoxon rank sum test, as appropriate.

The primary endpoint was to compare OS based on adjuvant RT dose level (standard vs high dose). The event for OS was death from any cause, and the interval was from diagnosis to date of death or last known alive.

Before matching, we performed a multivariable Cox proportional hazards model for OS including all predictor variables with backward stepwise selection ($P = .1$ to stay).

We used propensity score matching to reduce imbalance in predictor variables between the patient cohort receiving adjuvant standard-dose RT and those who received high-dose RT. Propensity scores were estimated with a multivariable logistic regression model in which adjuvant RT dose category (standard vs high) was regressed on all variables outlined in the Predictor Variables section. Propensity score matching used the nearest-neighbor method with a caliper distance of 0.2 without replacement to perform a 1:1 match between adjuvant RT dose levels.[12]

After matching, OS was estimated using the Kaplan-Meier method. The association between adjuvant RT dose and OS was evaluated using the Cox univariate proportional hazards model stratified by propensity score quintile. We also analyzed the association between RT dose category and OS in 2 prespecified subgroups of interest within the matched cohort: (1) astrocytoma histology and (2) 1p/19q noncodeleted.

Statistical analyses were performed using R version 3.2.5 and SPSS version 24 (IBM, Armonk, NY). All tests were 2-sided, and a P value $< .05$ was considered statistically significant.

Table 1 Patient and tumor characteristics for unmatched (n = 1043) and propensity score matched (n = 760) cohorts

Variable	Unmatched cohort			Matched cohort		
	Standard dose, n (%) or median (IQR)	High dose, n (%) or median (IQR)	*P* value	Standard dose, n (%) or median (IQR)	High dose, n (%) or median (IQR)	*P* value
N	644 (61.7%)	399 (38.2%)		380	380	
Facility type			.26			.85
Community	11 (1.7%)	13 (3.3%)		8 (2.1%)	10 (2.6%)	
Comprehensive community	91 (14.1%)	70 (17.5%)		55 (14.5%)	65 (17.1%)	
Academic/research	234 (36.3%)	134 (33.6%)		135 (35.5%)	129 (33.9%)	
Integrated network	67 (10.4%)	42 (10.5%)		39 (10.3%)	40 (10.5%)	
Unknown	241 (37.4%)	140 (35.1%)		143 (37.6%)	136 (35.8%)	
Sex			.72			.72
Male	372 (57.8%)	226 (56.6%)		212 (55.8%)	217 (57.1%)	
Female	272 (42.2%)	173 (43.4%)		168 (44.2%)	163 (42.9%)	
Race			.35			.97
White	584 (90.7%)	367 (92%)		349 (91.8%)	349 (91.8%)	
Black	31 (4.8%)	21 (5.3%)		19 (5%)	20 (5.3%)	
Other	29 (4.5%)	11 (2.8%)		12 (3.2%)	11 (2.9%)	
Insurance status			.72			.86
No insurance	45 (7%)	24 (6%)		19 (5%)	24 (6.3%)	
Private	452 (70.2%)	275 (68.9%)		270 (71.1%)	265 (69.7%)	
Government	142 (22%)	95 (23.8%)		87 (22.9%)	88 (23.2%)	
Unknown	5 (0.8%)	5 (1.3%)		4 (1.1%)	3 (0.8%)	
Median income by ZIP code			.53			.89
<$38,000	96 (14.9%)	64 (16%)		52 (13.7%)	59 (15.5%)	
$38,000-47,999	161 (25%)	89 (22.3%)		89 (23.4%)	88 (23.2%)	
$48,000-62,999	179 (27.8%)	103 (25.8%)		107 (28.2%)	101 (26.6%)	
≥$63,000	208 (32.3%)	143 (35.8%)		132 (34.7%)	132 (34.7%)	
No high school diploma by ZIP code			.42			.75
≥21%	96 (14.9%)	50 (12.5%)		50 (13.2%)	47 (12.4%)	
13%-20.9%	151 (23.4%)	87 (21.8%)		80 (21.1%)	85 (22.4%)	
7%-12.9%	233 (36.2%)	144 (36.1%)		146 (38.4%)	134 (35.3%)	
<7%	164 (25.5%)	118 (29.6%)		104 (27.4%)	114 (30%)	
Facility setting			.97			.96
Metro	513 (79.7%)	321 (80.5%)		306 (80.5%)	305 (80.3%)	
Urban	103 (16%)	62 (15.5%)		57 (15%)	59 (15.5%)	
Rural	12 (1.9%)	6 (1.5%)		5 (1.3%)	6 (1.6%)	
Unknown	16 (2.5%)	10 (2.5%)		12 (3.2%)	10 (2.6%)	
Charlson-Deyo comorbidity			.26			.84
0	538 (83.5%)	338 (84.7%)		326 (85.8%)	321 (84.5%)	
1	83 (12.9%)	41 (10.3%)		39 (10.3%)	41 (10.8%)	
≥2	23 (3.6%)	20 (5%)		15 (3.9%)	18 (4.7%)	
Year of diagnosis			<.001			.83
2004–2006	68 (10.6%)	93 (23.3%)		66 (17.4%)	75 (19.7%)	
2007–2009	128 (19.9%)	102 (25.6%)		102 (26.8%)	101 (26.6%)	
2010–2012	138 (21.4%)	83 (20.8%)		90 (23.7%)	83 (21.8%)	
2013-2015	310 (48.1%)	121 (30.3%)		122 (32.1%)	121 (31.8%)	
Chemotherapy type			.58			.27
Single agent	612 (695%)	374 (93.7%)		365 (96.1%)	356 (93.7%)	
Multiagent	15 (2.3%)	10 (2.5%)		4 (1.1%)	9 (2.4%)	
Unknown	17 (2.6%)	15 (3.8%)		11 (2.9%)	15 (3.9%)	
1p/19 status			<.001			.92
Codeleted	89 (13.8%)	26 (6.5%)		25 (6.6%)	26 (6.8%)	
Not codeleted	100 (15.5%)	36 (9%)		33 (8.7%)	36 (9.5%)	
Unknown	455 (70.7%)	337 (84.5%)		322 (84.7%)	318 (83.7%)	

(*continued on next page*)

Table 1 (*continued*)

Variable	Unmatched cohort			Matched cohort		
	Standard dose, n (%) or median (IQR)	High dose, n (%) or median (IQR)	*P* value	Standard dose, n (%) or median (IQR)	High dose, n (%) or median (IQR)	*P* value
Histology			<.001			.9
Astrocytoma	251 (39%)	216 (54.1%)		193 (50.8%)	199 (52.4%)	
Oligodendroglioma	223 (34.6%)	100 (25.1%)		109 (28.7%)	100 (26.3%)	
Mixed	148 (23%)	74 (18.5%)		70 (18.4%)	72 (18.9%)	
Glioma, not other specified	22 (3.4%)	9 (2.3%)		8 (2.1%)	9 (2.4%)	
Tumor size			.61			.76
≤5 cm	224 (34.8%)	151 (37.8%)		149 (39.2%)	140 (36.8%)	
>5 cm	212 (32.9%)	125 (31.3%)		115 (30.3%)	123 (32.4%)	
Unknown	208 (32.3%)	123 (30.8%)		116 (30.5%)	117 (30.8%)	
Extent of resection			< .001			.93
Subtotal	271 (42.1%)	122 (30.6%)		127 (33.4%)	122 (32.1%)	
Gross total	121 (18.8%)	49 (12.3%)		48 (12.6%)	49 (12.9%)	
Unknown	252 (39.1%)	228 (57.1%)		205 (53.9%)	209 (55%)	
Age (y)	43 (34–53)	45 (34–57)	.05	44 (35-54)	45 (34-56)	.44
Distance to facility (miles)	16.5 (7.3-38.2)	13 (6-32)	.05	14.7 (7.2-37.4)	13.1 (6.2-32)	.26
Median follow-up (mo)	38.4 (22.4-71.6)	41.1 (18.9-87.6)	.26	47.7 (22.7-87.2)	41.3 (19.6-85.9)	.41

Abbreviation: IQR = interquartile range.

Results

Patient characteristics

A total of 1043 patients were included in the cohort (Fig 1). Approximately 62% of patients received standard-dose RT and 38% received high-dose RT. Median RT dose in the standard-dose cohort was 54 Gy (IQR, 50.4–54), and it was 60 Gy in the high-dose cohort (IQR, 59.4–60). The vast majority of patients (95%) received single-agent chemotherapy. There were substantial missing data for tumor size (32% unknown), extent of resection (46% unknown), and LOH of 1p/19q (76%), which is common among NCDB studies of primary central nervous system (CNS) tumors.[13-16] Notably, extent of resection and 1p/19q codeletion status were not available for patients diagnosed before 2010. There were significant imbalances in several variables between the standard- and high-dose RT groups at baseline, including year of diagnosis, extent of resection, LOH of 1p/19q status, histology, age, and distance from home ZIP code to facility (Table 1). The median follow-up period for all patients was 38.9 months (IQR, 21.3–79.1). The median follow-up period for alive patients was 46.5 months (IQR, 24.4–88.3).

Survival analysis in unmatched cohort

The univariate OS analysis in the unmatched cohort demonstrated significantly higher OS for the standard-dose RT group compared with high dose, with 3-year OS of 84% versus 71.6% and 5-year OS of 72.1% versus 62.8%, respectively ($P = .004$). The multivariable model for OS in the unmatched cohort demonstrated older age, male sex, higher Charlson/Deyo comorbidity score, tumor size >5 cm, and astrocytoma histology as significantly associated with increased risk of death (Table 2). Adjuvant RT dose level (high vs standard dose) was not associated with OS (hazard ratio [HR], 1.2; $P = .1$).

Survival analysis in propensity score matched cohort

Propensity score matching yielded 380 pairs (n = 760) in the matched cohort. All variables were well balanced between RT dose level groups in the matched cohort (Table 1). The 3- and 5-year OS rates for standard-dose RT versus high-dose were not significantly different and were 80.9% versus 73.2% and 69% versus 63.8%, respectively ($P = .14$, Fig 2). RT dose level was also not associated with OS in Cox analysis stratified by propensity score quintile (HR, 1.2; 95% confidence interval, 0.94–1.52; $P = .15$). We also analyzed RT dose as a continuous variable in a sensitivity analysis, and the association was nonsignificant (HR, 1.02; $P = .19$).

Two subgroups of interest were analyzed, which included tumor types associated with worse prognosis and less chemotherapy sensitivity.[6] In the prespecified

Table 2 Multivariable analysis of overall survival in the unmatched cohort (n = 1043)

Variable	Hazard ratio	95% confidence interval	*P* value
Age (continuous)	1.03	1.03-1.04	<.001
Sex (female vs male)	0.76	0.6-0.95	.02
Insurance status			
No insurance	Reference		
Private	1.11	0.65-1.88	.71
Government	1.7	0.98-2.97	.06
Unknown	1.93	0.69-5.4	.21
Histology			
Astrocytoma	Reference		
Oligodendroglioma	0.38	0.29-0.51	<.001
Mixed	0.56	0.42-0.75	<.001
Glioma, NOS	0.51	0.25-1.03	.06
Charlson-Deyo comorbidity			
0	Reference		
1	1.18	0.85-1.63	.33
≥2	1.87	1.22-2.89	.004
Tumor size			
≤5 cm	Reference		
>5 cm	1.4	1.08-1.82	.01
Unknown	1.11	0.84-1.47	.47
RT dose level (high vs standard dose)	1.21	0.97-1.51	.1

Abbreviations: NOS = not otherwise specific; RT = radiation therapy.

astrocytoma histology subgroup (n = 392), there was no difference in OS between standard-dose versus high- dose RT, with 5-year OS of 57.6% versus 54.3%, respectively (P = .36, Fig 3). In the 1p/19q noncodeleted subgroup (n = 69), there was also no difference in OS by RT dose level, with 5-year OS of 66.7% versus 48.9%, respectively (P = .26).

Discussion

This NCDB retrospective cohort study included patients treated with adjuvant RT with concurrent and/or adjuvant chemotherapy for infiltrating LGG. We did not find any significant difference in OS for patients treated with standard-dose RT (45-54 Gy) and patients treated with high-dose RT (>54-65 Gy). Multivariable analysis did demonstrate older age, male sex, higher Charlson/Deyo comorbidity score, tumor size >5 cm, and astrocytoma histology as significant negative prognostic factors for OS in this patient population. We also did not observe a difference in OS between RT dose groups in the propensity matched cohort or within the 2 prespecified subgroups with less chemotherapy-sensitive disease and worse expected OS, specifically astrocytoma histology and 1p/19q noncodeleted.

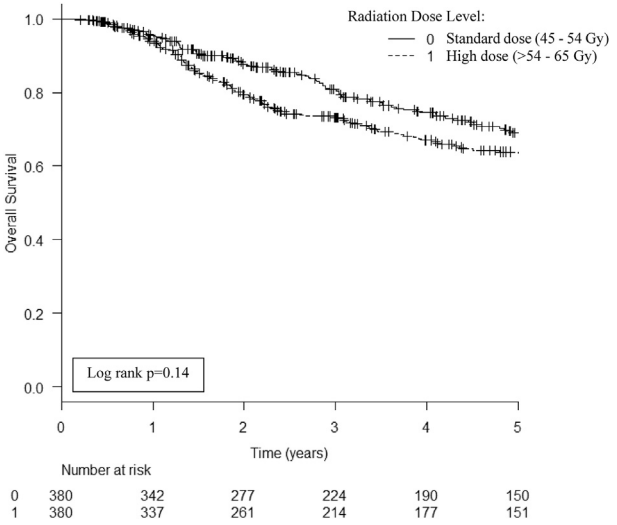

Figure 2 Overall survival by adjuvant radiation therapy (RT) dose level in the propensity matched cohort (n = 760).

The topic of RT dose with RT as adjuvant monotherapy was investigated in 2 seminal phase 3 studies. The US intergroup trial enrolled patients between 1986 and 1994, and pathology was centrally reviewed.[4] Patients were randomized to adjuvant 50.4 versus 64.8 Gy RT alone, with no benefit in PFS or OS demonstrated with higher-dose RT, but the rate of late grade ≥3 CNS toxicity was significantly higher with higher-dose RT (5-year 10% vs 2%; P = .04). Results were similar in the European Organization for Research and Treatment of Cancer trial, where patients were enrolled between 1985 to 1991 and randomized to adjuvant 45 versus 59.4 Gy RT alone.[3] Of note, there was no central pathology review of specimens on this trial. There was no difference in PFS

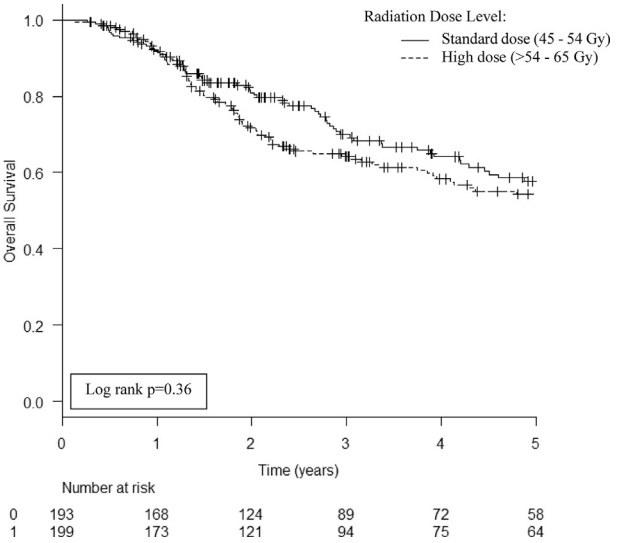

Figure 3 Overall survival by adjuvant radiation therapy (RT) dose level in the astrocytoma histology subgroup of the propensity matched cohort (n = 392).

or OS between arms, but no difference in late CNS toxicity either.

RTOG 9802 was then designed using an adjuvant RT dose of 54 Gy based on the majority opinion from a poll of radiation oncologists. High-risk patients (defined as not <40 years old with a GTR) were randomized between 1998 and 2002 to adjuvant RT ± PCV × 6 cycles.[6] Long-term outcomes demonstrated significant improvement in OS with the addition of PCV to RT independent of histology or IDH1 mutation status. However, only 56% of patients completed adjuvant chemotherapy per protocol, with the median number of adjuvant chemotherapy cycles only being 3 to 4 out of a planned 6. Owing to the toxicity of PCV and the contemporary use of TMZ in glioblastoma with tolerable toxicity,[17] there was extrapolation and adoption of the use of concurrent and/or adjuvant TMZ with RT for patients with LGG. This can be seen in the current study with the overwhelming use of single-agent (presumed to be TMZ) over multiagent chemotherapy. Evidence of efficacy for this regimen was provided by RTOG 0424, which was a phase 2 trial for patients with high-risk LGG who were treated with adjuvant RT to 54 Gy with concurrent and adjuvant TMZ.[7] Results demonstrated significantly improved 3-year OS compared with a historical control of high-risk patients treated on the European Organization for Research and Treatment of Cancer LGG trials. These data formed the basis of the current consensus recommendation for adjuvant RT with concurrent and/or adjuvant chemotherapy for high-risk patients.[9]

The goal of this study was to determine whether there was an association between OS and RT dose escalation for patients with infiltrative LGG when treated with the current standard of care of concurrent and/or adjuvant chemotherapy. Because we did not find a benefit of RT dose escalation above 54 Gy in the unmatched cohort, multivariable analysis, propensity score matched cohort, or prespecified subgroups of astrocytoma histology or 1p/19q noncodeleted, we do not recommend RT dose escalation above 54 Gy in this setting.

The limitations of this study are primarily due to its retrospective nature and include risk of patient selection bias, confounding by treatment indication due to nonrandomized use of escalated-dose RT, variable misclassification and/or miscoding due to the database structure, lack of central pathology review, relatively high levels of missing data for the variables of 1p/19q codeletion status, extent of resection, tumor size (frequent in NCDB studies of primary CNS tumors), and lack of cancer-specific survival and recurrence endpoints. Of note, the patient cases included in this study predate the 2016 World Health Organization change to use molecular definitions of LGG subtype and are based on histology.[18] The subgroups analyzed representing more chemotherapy-resistant disease (astrocytoma histology and 1p/19q noncodeleted) were small relative to the overall study population, and results should be interpreted with caution in this context. We also did not have IDH mutation status information as part of the database, which has also been shown to be a significant prognostic factor in LGG.[19] More detailed data on extent of resection, such as quantified extent of resection percentage, and postoperative/surveillance imaging modality used were not available. However, we used stringent patient selection criteria to produce a homogenous study population and employed multiple methods of adjustment, including multivariable analysis, propensity score matching, and stratification by histology and 1p/19q codeletion status, to minimize confounding risk. Use of these methods was possible due to the large study patient population and would not have been possible with smaller patient cohorts.

Conclusions

Patients with infiltrative grade 2 glioma treated with adjuvant RT with concurrent and/or adjuvant chemotherapy did not have an OS benefit with RT dose escalation above 54 Gy compared with 45 to 54 Gy in this large NCDB study. Methods to improve outcomes for poor-prognosis LGG, such as IDH wild-type astrocytoma, other than RT dose escalation should be considered.

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