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RESEARCH ARTICLE

Radiotherapy in adult low-grade glioma: nationwide trends in treatment and outcomes

R. S. Nunna[1] · S. Khalid[2] · J. S. Ryoo[1] · A. Sethi[1] · R. W. Byrne[3] · A. I. Mehta[1]

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Abstract

Background Management of WHO grade II gliomas (LGG) can include a combination of observation, surgery, radiotherapy (RT), and chemotherapy; however, optimal management remains unclear in regards to RT.

Objective The current study seeks to investigate the usage of RT in LGG and its effect on survival outcomes.

Methods Patients with diagnosis codes specific for LGG were queried from the National Cancer Database (NCDB) during the years 2004–2016. Kaplan–Meier curves with log-rank testing, univariate and multivariate Cox regression analysis, and comparisons of estimated 3- and 7-year survival were performed to investigate the effect of RT on overall survival.

Results 19,382 patients with LGG were identified with histologically confirmed disease. Kaplan–Meier testing demonstrated RT impacted survival in patients undergoing biopsy or no surgery ($p < 0.0001$), no chemotherapy ($p < 0.0001$), and in regimens with early RT ($p < 0.0001$) and high-dose RT ($p < 0.0001$). Cox multivariate regression demonstrated RT and age less than 40 (HR 0.93, 95% CI 0.89–0.97, $p = 0.001$), no chemotherapy (HR 0.82, 95% CI 0.77–0.87, $p < 0.001$), and astrocytoma histology (HR 0.72, 95% CI 0.66–0.79, $p < 0.001$) were associated with improved survival. 3-year survival of RT versus non-RT groups showed increased survival rates for age less than 40 years (+5.7%, $p < 0.0001$), no surgery or biopsy (+8.1%, $p < 0.0001$), no chemotherapy (+10.3%, $p < 0.0001$), mixed glioma (+6.7%, $p < 0.0001$), astrocytoma (+7.1%, $p < 0.0001$), and in regimens with early RT (+7.6%, $p < 0.0001$) and high-dose RT (+4.7%, $p < 0.0001$).

Conclusion This nationwide analysis of LGG patients found that RT was associated with improved survival outcomes in patients less than 40 years of age, with histology subtypes of astrocytoma and mixed glioma, undergoing biopsy or no surgery, and in regimens with early RT and high-dose RT.

Keywords Low grade · Glioma · Radiotherapy

Introduction

Gliomas are neuroepithelial tumors derived from supporting glial cells in the central nervous system [1]. The World Health Organization (WHO) Classification categorizes gliomas by grade (I–IV) and histologic subtype based on factors such as cellular atypia, anaplasia, mitotic activity, microvascular proliferation, necrosis, and genetic markers [1–3]. Low-grade gliomas (LGGs) are classified as grade I and II tumors and account for 5% of primary brain tumors and 15% of all gliomas [1, 2, 4, 5]. These tumors typically present between the second and fourth decades of life, with seizures present in up to 80% of patients [6]. WHO grade II gliomas consist of clinically, histologically, and molecularly heterogenous neoplasms grouped into astrocytic, oligodendroglial, mixed oligoastrocytic, and mixed glioneuronal tumors [2]. Although indolent in presentation, these tumors

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✉ A. I. Mehta
ankitm@uic.edu

[1] Department of Neurosurgery, University of Illinois at Chicago, 912 S. Wood Street, 451-N, Chicago, IL 60612, USA

[2] Department of Surgery, Rush University Medical Center, Chicago, IL 60612, USA

[3] Department of Neurosurgery, Rush University Medical Center, Chicago, IL 60612, USA

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are ultimately fatal and may cause significant morbidity. By virtue of the slow-growing nature of these tumors, the decision-making regarding therapeutic intervention is complicated, especially as it pertains to potential long-term side effects that may affect a patient's quality of life [7].

Management of WHO grade II gliomas can include a diverse combination of observation, surgical resection, radiotherapy (RT), and chemotherapy; however, the benefits of radiotherapy in this population have been controversial without a clear consensus in treatment [4, 6, 8, 9]. RT uses high-energy ionization radiation typically given to the patient in a series of treatments over weeks. In cases where surgical resection is ill-advised, such as eloquent cortex, RT is frequently recommended. Previous studies have suggested that patients with grade II glioma who are younger than 40 years should undergo magnetic resonance imaging (MRI) surveillance instead of RT, while those older than 40 years should be recommended RT [10]. Other studies have concluded that RT may prolong progression-free survival without a significant difference in overall survival [11, 12].

Despite various advances in treatment, the optimal management of patients with grade II gliomas is unclear and remains a clinical challenge, especially in regards to radiotherapy. The current study seeks to investigate current trends in the usage of radiotherapy in grade II gliomas in addition to elucidating the effect of these treatment strategies on survival outcomes.

Methods

Study cohort

The data for this study were derived from the National Cancer Database (NCDB), a prospectively collected cancer registry maintained jointly by the American College of Surgeons and the American Cancer Society. This database is sourced from over 1500 cancer centers and represents more than 70% of newly diagnosed cancer cases and more than 34 million historical records. Our study used the most recent release of the database available that provided patient data between the years 2004 and 2016.

For the purpose of our study, we specified our primary cohort of interest as all adult patients with primary intracranial LGG, including only WHO grade II tumors. We identified all histologic subtypes that would satisfy these criteria as classified by the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) as previously described [13]. This included all patients with the following confirmed histopathological diagnoses: glioma, NOS (9380), gliamatosis cerebri (9381), mixed glioma (9382), astrocytoma, NOS (9400), protoplasmic astrocytoma (9410), gemistocytic astrocytoma (9411), fibrillary astrocytoma (9420), pleomorphic xanthoastrocytoma (9424), and oligodendroglioma, NOS (9450). From the NCDB database, all patients with tumors originating from an intracranial site (primary site code C71.0-71.9) were first queried, and then screened for patients with the aforementioned ICD-O-3 diagnosis codes specifying LGG. We included only adults for which LGG was their first and primary tumor in addition to excluding all tumors that were not specifically coded as WHO grade II (collaborative stage site-specific factor 1). Subsequent tumors, recurrences, and cases without histopathological confirmation were not considered for this analysis.

NCDB data are publicly available and de-identified, and thus did not require review from our Institutional Review Board.

Statistical analysis

Descriptive analyses were performed to evaluate baseline patient and treatment characteristics, comparing RT and non-RT groups. Survival status was the variable employed to assess outcome and defined as either alive or not alive (i.e. all-cause mortality). This value was determined as the interval in months between the time of diagnosis and death or last follow-up as reported by NCDB. Survival analysis of various patient and treatment characteristic subgroups was performed in respect to this outcome measure.

The Student's t test was used for comparison of all continuous variables, while the Fisher exact test (or χ^2 test when appropriate) was used for all categorical variables. Kaplan–Meier curves were generated for comparative visualization of various demographic and treatment variables. All-inclusive multivariate Cox proportional hazard regression was used to analyze survival and adjust for confounding variables, with coefficients in the model converted to hazard ratios (HR) for analysis. Survival data were also used to compare estimated 3- and 7-year survival in RT and non-RT groups. All p values were reported as two-sided. Given the large number of statistical comparisons performed, a post hoc Bonferroni correction was employed in assessing statistical significance in each survival analysis to enhance the rigor of our investigation as previously described [14]. Statistical analysis was performed using R statistical software (version 3.4.0, 2017; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

Over the period evaluated, 19,677 adult primary intracranial grade II glioma patients were identified and grouped

by histologic subtype and ICD-O-3 diagnosis code (Supplemental Table 1). 295 patients lacked information regarding radiation treatment and were excluded from further analysis. The most common histology types were astrocytic lineage tumors ($n=8492$, 43.8%), followed by oligodendroglioma ($n=5996$, 30.9%) and mixed or NOS ($n=4894$, 25.3%) (Table 1). Most patients were greater than age 40 ($n=11{,}305$, 58.3%), male ($n=10{,}895$, 56.2%), and white ($n=17{,}076$, 89.4%). Biopsy or no surgery was the most common surgical intervention ($n=7172$, 37.0%), followed by surgical resection with unknown margins (NOS) ($n=6873$, 35.5%). Chemotherapy was not administered for the majority of patients ($n=12{,}598$, 65.0%), followed by single-agent therapy ($n=5213$, 26.9%). Chemotherapy was started at an average of 74.3 days (SD: 109.2) after diagnosis.

When discerning by radiation status, histology ($p<0.001$), age ($p<0.001$), sex ($p=0.001$), extent of resection ($p<0.001$), and chemotherapy status ($p<0.001$) were significantly different between groups. There was no difference in the timing for initiation of chemotherapy between these groups ($p=0.079$). Subgroups with the highest rates of radiotherapy included patients undergoing chemotherapy (71.3%), patients that underwent biopsy or no surgery (49.2%), patients over the age of 40 (46.4%), and astrocytoma (47.0%) and mixed glioma patients (42.3%). The lowest rates of radiotherapy were found in patients that underwent gross total resection (GTR) (25.0%), followed by oligodendroglioma patients (27.5%) and patients under the age of 40 (30.5%).

The majority of patients did not undergo RT (59.3%) (Supplemental Table 2). RT was started at an average of 68.7 days (SD 97.5) after diagnosis, with a mean dose of 5108 cGy (SD 2573). A minority of those undergoing RT also underwent a boost treatment (23.0%), with a mean dose of 302 cGy (SD 821). RT was performed over an average of 41.9 days (SD 14.1), with an average of 30.2 treatment volumes (SD 23.7). External beam RT of unspecified or various energy wavelengths was the most common modality (49.6%).

Table 1 Baseline characteristics of low-grade glioma in adults

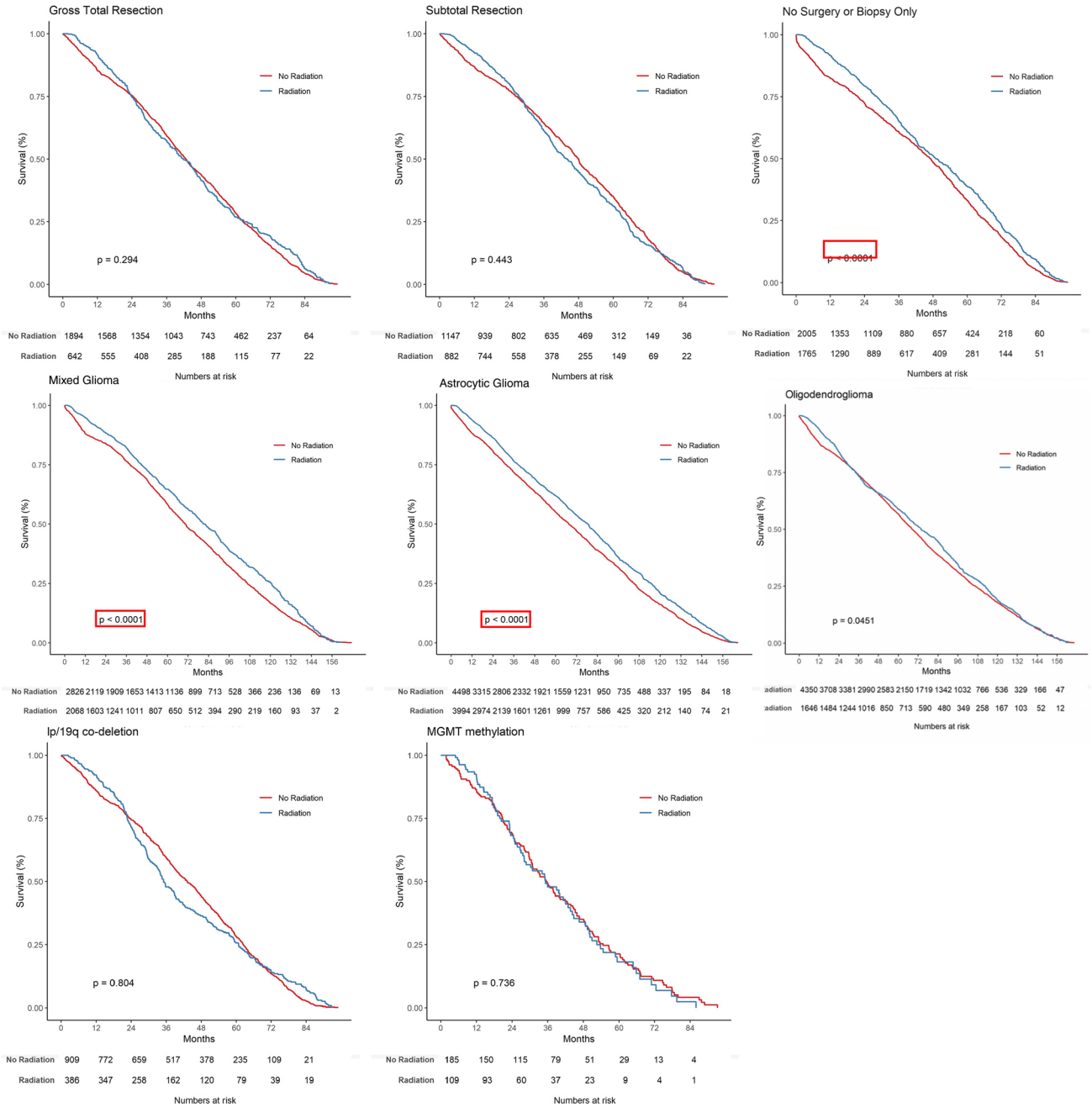
Characteristics	Total ($N=19{,}382$)	Radiation ($N=7708$)	No radiation ($N=11{,}674$)	p
Histology				<0.001*
Mixed glioma, *n* (%)	4894 (25.3)	2068 (26.8)	2826 (24.2)	
Astrocytoma, *n* (%)	8492 (43.8)	3994 (51.8)	4498 (38.5)	
Oligodendroglioma, *n* (%)	5996 (30.9)	1646 (21.4)	4350 (37.3)	
Age				<0.001*
<40 years, *n* (%)	8077 (41.7)	2464 (32.0)	5613 (48.1)	
>40 years, *n* (%)	11,305 (58.3)	5244 (68.0)	6061 (51.9)	
Sex				0.001*
Male, *n* (%)	10,895 (56.2)	4444 (57.7)	6451 (55.3)	
Female, *n* (%)	8487 (43.8)	3264 (42.4)	5223 (44.7)	
Race				0.014
White, *n* (%)	17,076 (89.4)	6819 (89.6)	10,257 (89.3)	
Black, *n* (%)	1320 (6.4)	510 (6.7)	720 (6.3)	
Other, *n* (%)	790 (4.1)	278 (3.65)	512 (4.5)	
Surgical extent of resection				<0.001*
Gross total resection, *n* (%)	2863 (14.8)	715 (9.3)	2148 (18.4)	
Subtotal resection, *n* (%)	2474 (12.8)	1030 (13.4)	1444 (12.4)	
Biopsy or no surgery, *n* (%)	7172 (37.0)	3531 (45.8)	3641 (31.2)	
NOS, *n* (%)	6873 (35.5)	2432 (31.6)	4441 (38.0)	
Chemotherapy				<0.001*
Single-agent, *n* (%)	5213 (26.9)	3738 (48.5)	1475 (12.6)	
Multi-agent, *n* (%)	420 (2.2)	304 (3.9)	116 (1.0)	
Agent NOS, *n* (%)	375 (1.9)	245 (3.2)	130 (1.1)	
Unknown, *n* (%)	776 (4.0)	188 (2.4)	588 (5.0)	
None, *n* (%)	12,598 (65.0)	3233 (41.9)	9365 (80.2)	
Started days after diagnosis, mean (SD)	74.3 (109.2)	72.4 (108.1)	75.5 (110.0)	0.079

NOS not otherwise specified

*Statistically significant ($p<0.007$) after Bonferroni post-hoc correction for multiple comparisons ($n=7$)

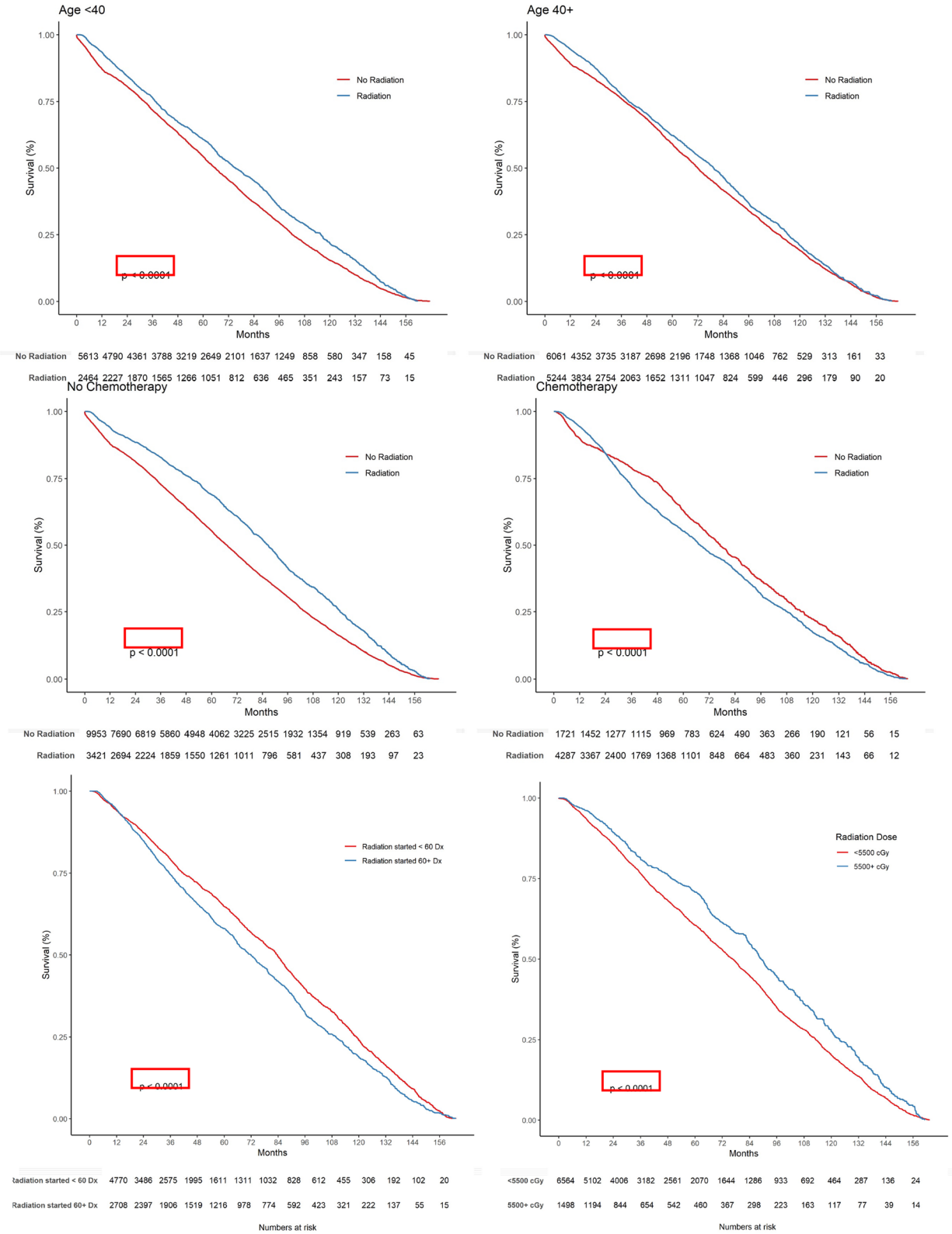
Survival analysis

Kaplan–Meier (KM) log-rank testing showed that RT was associated with improved survival outcomes in patients undergoing biopsy or no surgery ($p < 0.0001$), while failing to show any association of survival outcomes with RT in GTR ($p = 0.294$) and subtotal resection (STR) patients ($p = 0.443$) (Fig. 1). Analysis by histology showed that radiation improved survival outcomes in mixed glioma ($p < 0.0001$) and astrocytoma ($p < 0.0001$), but not in oligodendroglioma ($p = 0.0451$). KM testing did not show an association of survival outcomes with RT in patients with 1p/19q co-deletion ($p = 0.804$) or MGMT methylation ($p = 0.736$). RT was associated with improved survival outcomes in all age groups ($p < 0.0001$) (Fig. 2). A subgroup analysis by chemotherapy status demonstrated that RT was



Statistically significant (red box) (p<0.0036) after Bonferroni post-hoc correction for multiple comparisons (n=14)

Fig. 1 Kaplan–Meier survival analysis by surgical extent of resection, histology, and genetic marker. **a** Gross total resection. **b** Subtotal resection. **c** No surgery or biopsy only. **d** Mixed or NOS. **e** Astrocytoma. **f** Oligodendroglioma. **g** 1p/19q co-deletion. **h** MGMT methylation



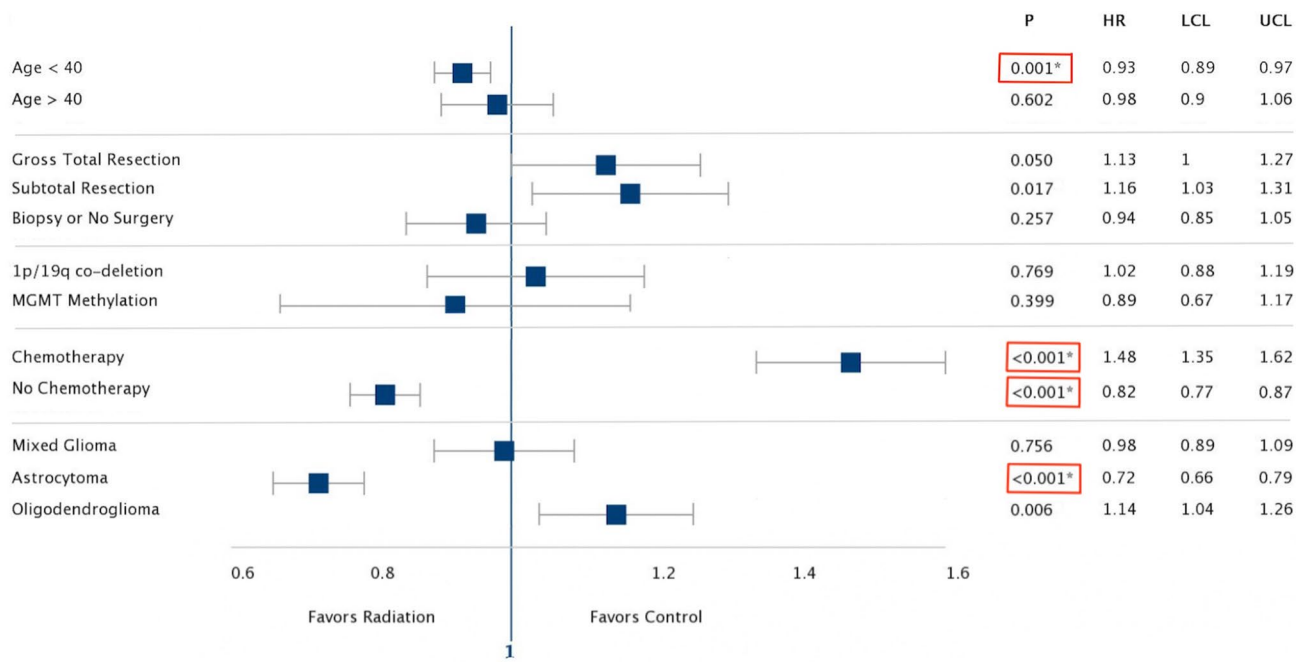
Statistically significant (red box) (p<0.0036) after Bonferroni post-hoc correction for multiple comparisons (n=14)

Fig. 2 Kaplan–Meier survival analysis by age, chemotherapy status, and radiation parameters. **a** Age < 40. **b** Age > 40. **c** No chemotherapy. **d** Chemotherapy. **e** Radiation timing. **f** Radiation dose

associated with improved survival outcomes in patients not receiving chemotherapy ($p < 0.0001$), while it was associated with worsened overall survival in patients receiving chemotherapy ($p < 0.0001$). Finally, an analysis of radiation parameters revealed that radiation started less than 60 days after diagnosis was associated with improved survival outcomes ($p < 0.0001$), while a dose greater than 5500 cGy was similarly associated with improved survival status ($p < 0.0001$).

Radiation in patients less than 40 years of age ($p < 0.001$) was associated with improved survival status in univariate (HR 0.89, 95% CI 0.86–0.93, $p < 0.001$) and multivariate regression (HR 0.93, 95% CI 0.89–0.97, $p = 0.001$) (Fig. 3, Supplemental Table 3). However, we did not find a benefit of RT in patients greater than age 40, contrary to KM testing. Radiation and neither extent of resection nor genetic markers were found to have a significant association with survival outcomes. RT with chemotherapy was associated with worsened survival outcomes in univariate (HR 1.61, 95% CI 1.47–1.76, $p < 0.001$) and multivariate regression (HR 1.48, 95% CI 1.35–1.62, $p < 0.001$). However, RT in patients not receiving chemotherapy was associated with improved survival outcomes in both univariate (HR 0.82, 95% CI 0.77–0.88, $p < 0.001$) and multivariate regression (HR 0.82, 0.77–0.87, $p < 0.001$). RT in astrocytoma patients was associated with improved survival outcomes in both univariate (HR 0.81, 95% CI 0.76–0.86, $p < 0.001$) and multivariate regression (HR 0.72, 0.66–0.79, $p < 0.001$). RT in oligodendroglioma patients was associated with worsened overall survival in univariate analysis (HR 1.16, 95% CI 1.06–1.28, $p = 0.001$), while this effect was lost in multivariate analysis.

3-Year survival analysis demonstrated increased survival rates in comparing RT and non-RT groups for age less than 40 years (+5.7%, $p < 0.0001$), age greater than 40 years (+4.3%, $p < 0.0001$), no surgery or biopsy (+8.1%, $p < 0.0001$), no chemotherapy (+10.3%, $p < 0.0001$), mixed glioma (+6.7%, $p < 0.0001$), astrocytoma (+7.1%, $p < 0.0001$), and regimens with early RT (+7.6%, $p < 0.0001$) and high-dose RT (+4.7%, $p < 0.0001$) (Table 2). While analysis of 7-year survival was subject to limitations on follow-up, the same comparisons found increased survival rates in age less than 40 years (+13.7%, $p < 0.0001$), age greater than 40 years (+12.8%, $p < 0.0001$), no surgery or biopsy (+20.4%, $p < 0.0001$), no chemotherapy (+19.4%, $p < 0.0001$), mixed glioma (+14.6%, $p < 0.0001$), astrocytoma (+15.3%, $p < 0.0001$), and regimens with early RT (+15.6%, $p < 0.0001$) and high-dose RT (+10.0%, $p < 0.0001$).



*Statistically significant (red box) (p<0.004) after Bonferroni post-hoc correction for multiple comparisons (n=12); HR, hazard ratio; LCL, lower 95% confidence level; UCL, upper 95% confidence level

Fig. 3 Forest plot showing multivariate Cox regression analysis of the effect of radiation treatment on patient survival by subgroup

Table 2 3- and 7-year survival comparison by radiation status and radiotherapy parameters

Characteristics (RT vs. non-RT)	3-Year survival		7-Year survival	
	Δ (%)	*p*	Δ (%)	*p*
Age < 40	+ 5.7	< 0.0001*	+ 13.7	< 0.0001*
Age > 40	+ 4.3	< 0.0001*	+ 12.8	< 0.0001*
Gross total resection	+ 1.7	0.4483	+ 14.7	< 0.0001*
Sub-total resection	+ 1.1	0.5728	+ 15.6	< 0.0001*
No surgery or biopsy	+ 8.1	< 0.0001*	+ 20.4	< 0.0001*
Chemotherapy	− 0.6	0.6081	+ 8.7	< 0.0001*
No chemotherapy	+ 10.3	< 0.0001*	+ 19.4	< 0.0001*
1p/19q co-deletion	− 9.2	0.0023	+ 11.2	< 0.0001*
MGMT methylation	+ 2.5	0.6837	+ 11.7	0.0225
Mixed glioma	+ 6.7	< 0.0001*	+ 14.6	< 0.0001*
Astrocytoma	+ 7.1	< 0.0001*	+ 15.3	< 0.0001*
Oligodendroglioma	+ 1.0	0.4422	+ 10.1	< 0.0001*
Radiotherapy parameters	Δ (%)	*P*	Δ (%)	*p*
Early RT (< 60 days) vs late RT (> 60 days)	+ 7.6	< 0.0001*	+ 15.6	< 0.0001*
Low-dose RT (< 5500 cGy) vs. High-dose RT (> 5500 cGy)	− 4.7	< 0.0001*	− 10.0	< 0.0001*

RT radiotherapy

*Statistically significant ($p < 0.0017$) after Bonferroni post hoc correction for multiple comparisons ($n = 28$)

Discussion

WHO grade II gliomas consist of clinically, histologically, and molecularly heterogenous neoplasms largely grouped into astrocytic, oligodendroglial, mixed oligoastrocytic, and mixed glioneuronal tumors [2]. Although indolent in initial presentation, grade II gliomas ultimately have a fatal outcome and may cause considerable morbidity. By virtue of the slow-growing nature of these tumors, the decision-making regarding therapeutic intervention is complicated, especially as it pertains to potential long-term side effects that may affect a patient's quality of life [7]. Imaging plays a critical role in the diagnosis of grade II gliomas, especially in differentiation between higher grade lesions [15]. Advanced emerging imaging techniques such as arterial spin labeling in MR perfusion studies show great potential in aiding in accurate diagnosis [16–18]. There has been an array of clinical trials regarding RT in this population to determine which subgroups may benefit from such treatment, as well as the timing of treatment and its efficacy within a multimodal treatment paradigm; even so, the optimal role of RT in grade II glioma remains unclear. Thus, we attempt to elucidate the efficacy of RT in different populations and describe prognostic factors related to this intervention through the analysis of a large, national database.

The current study represents the largest and most comprehensive retrospective analysis of radiotherapy in adult primary LGGs conducted to date. This study is also unique in that several thoughtful subgroup analyses have been performed for further analysis of the optimal populations that may benefit from radiotherapy, in addition to comparing to current indications. In a series of 19,382 patients, our results underscore the immense variability in current treatment trends nationwide. Overall, we found that current usage patterns reflect previously suggested prognostic factors, with the greatest rates of radiotherapy employed in patients with astrocytic and mixed glioma histologies, patients over the age of 40, and patients undergoing biopsy or no surgery. General prognostic factors of grade II gliomas have previously been described in terms of patient and tumor characteristics, and subsequently used as an indicator that a patient should be considered for adjuvant therapy. Pignatti et al. performed a multivariate analysis with data from two European Organization for Research and Treatment of Cancer (EORTC) trials (EORTC 22844 and EORTC 22845) and derived a prognostic scoring system with five unfavorable prognostic factors for survival: (1) age ≥ 40 years, (2) astrocytoma histology subtype, (3) tumor diameter ≥ 6 cm, (4) tumor crossing the midline, and (5) presence of neurological deficits before surgery. The presence of up to two of these factors identified a low-risk group, which displayed a median overall survival of 7.7 years, whereas three or more factors identified a high-risk group with a median survival of 3.2 years [19]. Our results validate this histology-based component for decision making, finding that patients with astrocytic gliomas demonstrated the greatest benefit from

RT, followed by mixed gliomas. RT in oligodendroglioma was not found to conclusively improve outcomes. Previous studies have also used patients that have undergone subtotal resection as an indication for adjuvant therapy [9]. RT was found to generally have a greater effect on outcomes in patients that had undergone biopsy only or no surgery in our analysis. Overall, our findings suggest that this constellation of high-risk features have largely been followed for decision-making regarding radiotherapy.

The results of our analysis, however, suggest that patients less than the age of 40 may also benefit from RT in regards to overall survival, significantly improving both 3- and 7-year survival. This finding is in contrast to these previous assessments that indicate that age greater than 40 is a high-risk feature that may warrant up-front adjuvant treatment [20]. This survival benefit does not take into account potential side effects such as neurocognitive decline, which should be carefully weighed in younger patients. We did not find available genetic markers (1p/19q co-deletion and MGMT methylation) to be prognostic factors for the usage of RT. However, several genetic alterations have been previously shown to possess prognostic value in regards to overall survival. For example, the presence of combined deletions of chromosome arms 1p and 19q denotes a favorable prognosis in pure oligodendrogliomas [21–23]. Similarly, mutations in IDH1/2 are associated with longer overall survival regardless of histopathological subtype [24, 25]. However, our findings suggest that the genetic markers we have investigated have unclear value in decision-making for radiotherapy.

Regimens with high-dose RT were associated with improved survival outcomes in all assessments in our analysis. These findings were in contrast to several previous prospective clinical trials that have demonstrated the lack of a radiotherapeutic dose–response relationship in grade II glioma. The EORTC trial 22844 randomized 379 adults with LGG into a low-dose arm of 45 Gy in 5 weeks and a high-dose arm of 59.4 Gy in 6.6 weeks after surgery or biopsy. There was no significant difference in terms of 5-year OS (58% vs. 59%, respectively) or 5-year PFS (47% vs. 50%, respectively) between the two groups [12]. A similar study which randomized 203 patients into low-dose (50.4 Gy in 28 fractions) and high-dose (64.8 Gy in 36 fractions) arms also showed no significant difference in survival at 2 years (94% and 85%, respectively) and 5 years (72% and 64%, respectively) [27]. Notably, there was a higher 2-year actuarial incidence of radiation neurotoxicity in the high-dose RT arm (5% vs. 2.5%) [27].

Similarly, regimens with early RT were also associated with significantly improved survival outcomes in our analysis. The optimal timing of RT is a complex issue which requires a balance between achieving favorable tumor control and limiting side-effects that can degrade a patient's quality of life. The EORTC 22845 study randomized 314 patients into an early postoperative RT group and a deferred treatment group, which postponed any postoperative treatment until recurrence. Although the early RT group had an improved median PFS (3.4 years vs. 5.3 years) and a reduced occurrence of seizures (25% versus 41%, respectively), median OS remained similar between the two groups (7.4 years versus 7.2 years) [11]. The observed lack of benefit in OS has crucial implications, especially against the backdrop of increased risk of long-term cognitive dysfunction with prolonged RT [28, 29]. Indeed, in a 12-year follow-up study of grade II glioma patients, those who underwent RT were found to demonstrate a decline in attentional functioning, executive functioning, and information processing speed, along with correlative radiological abnormalities such as white-matter hyperintensities and global cortical atrophy [30, 31]. These findings give some credence to the argument for delaying RT in healthy, low-risk patients until clinically necessary [32, 33]. In a large series of patients, however, our findings challenge previous notions that there is no difference in survival outcomes in regards to both timing and dose of RT, and requires further robust prospective investigation.

Our findings also suggest that RT was most beneficial in patients not undergoing chemotherapy. Interestingly, the opposite was found to be true for patients undergoing both chemotherapy and radiotherapy in all assessments. This finding can likely be attributed to selection bias as patients with the most aggressive disease are inherently predisposed to the most aggressive treatment paradigms. However, the combined toxicity of multiple treatment modalities may also be considered and requires further research. Overall, our analysis suggested an unclear role for RT in combination with chemotherapy. Previous investigations have hypothesized that the addition of chemotherapy to a treatment regimen consisting of maximal surgical excision with post-operative RT may provide an increased survival benefit. The Radiation Therapy Oncology Group (RTOG) 9802 trial, a phase 3 trial of 251 patients followed for a median of 11.9 years, compared survival of patients who received postoperative RT with or without 6 cycles of adjuvant procarbazine, lomustine, and vincristine (PCV) treatment. Patients who received chemoradiotherapy (CRT) had longer median OS compared to those received only RT (13.3 years vs. 7.8 years, respectively) as well as improved median PFS (10.4 years vs. 4.0 years, respectively) [34]. Even when compared to studies observing survival benefits of chemotherapy monotherapy, CRT with PCV seemingly provides a benefit with increased PFS and OS [20, 35, 36]. In light of the efficacy of CRT with PCV, adjuvant temozolomide (TMZ) with RT has also been investigated. Often utilized with proven efficacy in high-grade gliomas, TMZ affords the benefits of good penetration of the blood–brain barrier as well as oral administration and favorable toxicity profile when compared with PCV [37]. To date, the RTOG 0424 trial has been the only study which has

observed the efficacy of CRT using TMZ. In a preliminary analysis, the 3-year OS rate of 73.1% was shown to be higher when compared to historical controls treated with RT only during previous clinical trials EORTC 22844 and EORTC 22845 [38].

Limitations

Our study is subject to several limitations which must be considered when interpreting our results. The use of NCDB, a large, registry-based dataset, renders our analysis vulnerable to factors that are not routinely collected, thus were unable to be controlled for. For example, specific chemotherapeutic agents and doses were unavailable and thus could not be included for analysis. The standard treatment regimen employed by many cancer centers was transitioning from PCV to temozolomide during the time period of the current study, potentially confounding survival analysis. In addition, usage of a large database is also vulnerable to inaccuracy or inconsistencies in reporting. A large portion of patients were reported to have unknown surgical margins and were thus excluded from survival analysis in regards to extent of resection. Moreover, the significant portion of patients undergoing biopsy only or no surgery may be secondary to inconsistencies in facility reporting, as anecdotal experience suggests a lower percentage. Furthermore, biopsy itself in this patient population is susceptible to grading error, with different regions of the same tumor potentially demonstrating different grades.

The retrospective nature of the study also leaves us unable to control for pre-intervention disease state. More aggressive treatment paradigms are generally recommended to patients with the worst prognoses, contributing to selection bias. In addition, there exist significant variability in the treatment patterns of neurosurgeons, neurooncologists, and radiation oncologists. Finally, while the current study assesses data over a 13-year period, extent of resection and genetic markers were only available for the last 7 years of this period. Consequently, survival analysis for these groups is especially subject to significant variability. Moreover, a large portion of our entire cohort may have follow-up data of less than 10 years due to the year of diagnosis, also limiting the interpretation of our analysis.

Despite these drawbacks, our study provides a description of the usage of radiotherapy in the largest sample of LGG patients to date. Although definitive evidence regarding the efficacy of treatment regimens should be elucidated from robust, prospective trials, our analysis has inherent value in illustrating and validating survival trends on a large scale. Prudent future research would also focus on other experimental therapies that may be even more efficacious than current treatment modalities [26].

Conclusion

In the largest study to date, this nationwide analysis of adult LGG patients found that RT was associated with improved survival outcomes in patients less than 40 years of age, with histology subtypes of astrocytoma and mixed glioma, undergoing biopsy or no surgery, and not undergoing chemotherapy. In addition, early RT and high-dose RT were both associated with improved survival outcomes.

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Compliance with ethical standards

Conflict of interest The author(s) declare that they have no competing interests.

Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors.

Research involving human participants and/or animals informed consent NCDB data are publicly available and de-identified, and thus did not require review from our Institutional Review Board.

Informed consent For this type of study formal consent is not required.

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