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Impact of radiotherapy delay following biopsy for patients with unresected glioblastoma

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OBJECTIVE Because of the aggressive nature of glioblastoma, patients with unresected disease are encouraged to begin radiotherapy within approximately 1 month after craniotomy. The aim of this study was to investigate the potential association between time interval from biopsy to radiotherapy with overall survival in patients with unresected glioblastoma.

METHODS Patients with unresected glioblastoma diagnosed between 2010 and 2014 who received adjuvant radiotherapy and concurrent chemotherapy were identified in the National Cancer Database. Demographic and clinical data were compared using chi-square and Wilcoxon rank-sum tests. Survival was analyzed using the Kaplan-Meier method and Cox proportional hazards regression modeling.

RESULTS Among 3456 patients with unresected glioblastoma, initiation of radiotherapy within 3 weeks of biopsy was associated with a higher hazard of death compared with later initiation of radiotherapy. After excluding patients who received radiotherapy within 3 weeks of biopsy to minimize the effects of confounders associated with short time intervals from biopsy to radiotherapy, the median interval from biopsy to radiotherapy was 32 days (IQR 27–39 days). Overall, 1782 (66.82%) patients started radiotherapy within 5 weeks of biopsy, and 885 (33.18%) patients started radiotherapy beyond 5 weeks of biopsy. On multivariable analysis, there was no significant difference in overall survival between these two groups (HR 0.96, 95% CI 0.88–1.50; p = 0.374).

CONCLUSIONS In patients with unresected glioblastoma, a longer time interval from biopsy to radiotherapy does not appear to be associated with worse overall survival. However, external validation of these findings is necessary given that selection bias is a significant limitation of this study.

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KEYWORDS glioblastoma; timing of radiation; biopsy only; survival; oncology

Glioblastoma is one of the most common and highly challenging CNS malignancies, with a 5-year survival rate of approximately 5%.[1,2] The current treatment paradigm for this disease was established in 2005 by the EORTC-NCIC (European Organisation for Research and Treatment of Cancer–National Cancer Institute of Canada) trial and involves maximal safe resection of the tumor followed by radiotherapy and temozolomide.[3,4] Since then, there have been extensive ongoing efforts toward developing a more personalized treatment approach, which has led to a new prognostication system based on genomic criteria as well as increased hope for the emergence of effective targeted therapies.[5,6] However, patient outcomes remain dismal in the meantime, with median overall survival (OS) rates hovering at around 20 months.[4,7,8]

There is a significant need for further optimization of the current treatment regimen, particularly for the 15%–30% of patients who are unable to undergo resection. These patients remain an understudied group despite having the worst prognosis among all glioblastoma patients.[9] Although patients who receive a biopsy instead of a resection have significantly lower OS and experience greater neurological and functional deterioration, there is limited information on how to improve management for biopsy-only patients.[10]

ABBREVIATIONS IDH = isocitrate dehydrogenase; KPS = Karnofsky Performance Status; MGMT = O^6-methylguanine-DNA methyltransferase; NCDB = National Cancer Database; OS = overall survival.

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In particular, the importance of the timing of adjuvant radiotherapy for patients with unresected glioblastoma remains unclear. Because of the aggressive nature of glioblastoma, it is common practice to start radiotherapy within approximately 1 month after biopsy or even sooner in cases in which patients are perceived to have more extensive disease burden. However, there are no high-quality data to support this in patients who do not undergo resection specifically. Despite this, data on the timing of postoperative radiotherapy have been mostly retrospective and have led to conflicting results, and very few studies have examined this subject in the unresected population.[11] There may be delays in treatment initiation depending on circumstances, such as complex treatment planning or the effects of the COVID-19 pandemic on either the patient or the treating radiation oncology department. Therefore, our goal was to explore the potential association between timing of radiotherapy initiation and survival outcomes in patients undergoing biopsy only using a large national database.

Methods

Data Source

The National Cancer Database (NCDB), a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society, was used to conduct this retrospective study. Cancer registry records from more than 1500 accredited hospitals and approximately 70% of newly diagnosed cancers in the United States are captured by the NCDB.[12] The Commission on Cancer of the American College of Surgeons and the American Cancer Society are not responsible for the statistical methodology or the conclusions drawn from this study. The Yale Human Investigation Committee granted an exemption for this study.

Variables recorded in the database include clinical/tumor characteristics, socioeconomic status, patient demographics, Karnofsky Performance Status (KPS), and details on all modalities of treatment administered to the patient before disease progression or recurrence. Of note, details regarding chemotherapy type, radiation fields, and treatment duration were not available.

Study Cohort

Within the NCDB, we identified patients diagnosed with glioblastoma from 2010 to 2014 who received a histological diagnosis and a biopsy but did not receive resection (Facility Oncology Registry Data Standards code 20). Inclusion and exclusion criteria are summarized in Fig. 1. Patients who did not receive single-agent chemotherapy concurrently with external-beam radiation therapy (concurrent treatment was defined as chemotherapy and radiotherapy starting within 14 days of each other) were excluded. The relationship between the natural logarithm of the hazard ratio and the time from biopsy to radiotherapy was plotted. A sensitivity analysis in which patients who received radiation 0–3 weeks after biopsy were excluded is shown in Supplemental Data. Patients who received radiotherapy within 3 weeks of biopsy were subsequently excluded, as it is likely that these patients had unfavorable clinical factors that could not be measured in the NCDB. Patients who died within 2 months of biopsy were excluded to account for immortal time bias. This cutoff point was chosen because 2 months is the estimated amount of time it would take for a patient to complete a course of radiotherapy to 60.00 Gy when accounting for a typical radiation planning time of 2 weeks. To assess the robustness of our results using this cutoff point, we conducted a sequential landmark analysis by excluding patients who died 0–6 months postbiopsy. A sensitivity analysis, in which patients who died within 2 months of biopsy; received radiotherapy within 3 weeks of surgery; and did not receive 40.00 Gy in 15 fractions, 40.05 Gy in 15 fractions, or 60.00 Gy in 30 fractions were excluded, was performed and the results can be found in Supplemental Data.

Variables

Regarding patient demographics, age was evaluated as a continuous variable; race was categorized as White, Black/African American, or other; and sex was dichotomized as male or female. Patients were dichotomized as living in an urban location (county population ≥ 250,000) versus nonurban location (population < 250,000) and having private versus nonprivate insurance. Household income was recorded in quartiles of 2012 adjusted household annual income of the patient's area of residence and dichotomized as ≥ $63,000 or < $63,000. Performance status was derived from the KPS score and categorized as 0–40, 50–70, and 80–100.

As for tumor characteristics, O^6-methylguanine-DNA methyltransferase (MGMT) status was classified as methylated, unmethylated, or unknown. Tumor size was evaluated as a continuous variable.

Regarding treatment facility data, facility types were assigned according to the Commission on Cancer accreditation category based on annual case volume and available oncology services and were dichotomized as academic or nonacademic (including community cancer programs and comprehensive community cancer programs). Treatment location was categorized as Northeast, Midwest, South, and West.

Statistical Analysis

Categorical variables were compared using chi-square tests, and continuous variables were compared using Wilcoxon rank-sum tests. OS, defined as the time from biopsy to death, was the primary endpoint. The patient cohort was dichotomized into two groups based on time interval from biopsy to radiotherapy. OS was plotted on Kaplan-Meier curves, and the log-rank test was used to assess for differences in outcomes. Backward stepwise Cox regression was used to conduct multivariable survival analyses. Variables were included in the initial multivariable model only if they were found to be associated with survival ($p < 0.05$) in univariable analysis or if determined a priori to be clinically relevant.

To account for potential differences in radiation dose between patients who started radiation soon after biopsy versus those who started later, we conducted a sensitivity analysis in which we restricted the study sample to only patients who received standard doses of 40.00 Gy in 15

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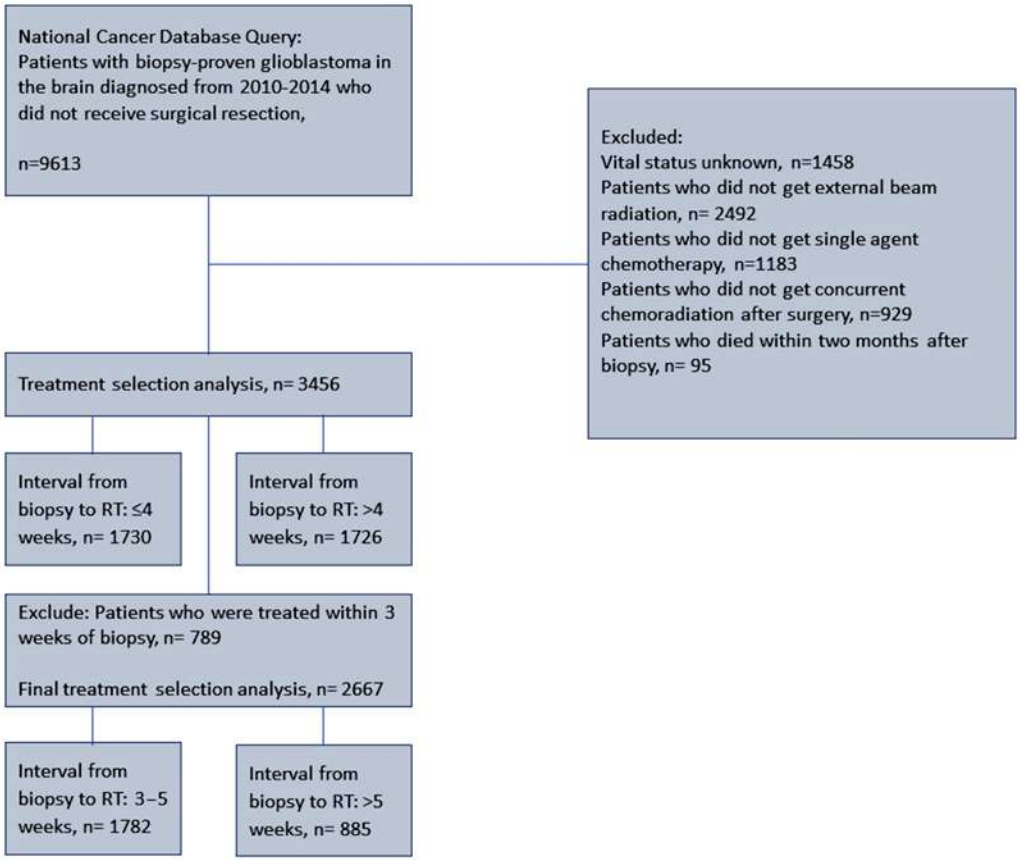

FIG. 1. Inclusion and exclusion criteria. Figure is available in color online only.

fractions, 40.05 Gy in 15 fractions, or 60.00 Gy in 30 fractions. Additionally, a sequential landmark analysis was performed by selecting monthly landmarks from 1 to 6 months after the biopsy to assess the robustness of our results from the primary analysis.

We also conducted a second sensitivity analysis looking at patients without excluding those who received radiotherapy within 3 weeks of biopsy and plotted the natural log of the HR in relation to time elapsed after surgery to better account for the relationship between survival outcome and time to radiotherapy.

Finally, to assess if our results were robust despite the presence of missing data, we performed multiple imputation using the *mice* package in R. We generated 5 imputed data sets and ran Cox proportional hazards models on each of the data sets. The pooled estimates were calculated to obtain the values for the average regression coefficients and corrected 95% confidence intervals. All tests of significance were two-sided. All analyses were performed using Stata SE 13.1 (Stata Corp.).

Results

Study Cohort Characteristics

A total of 9613 patients with biopsy-proven glioblastoma without resection were identified. Patients were excluded if they had unknown vital status (n = 1458), did not receive external-beam radiation therapy (n = 2492), did not receive single-agent chemotherapy (n = 1183), did not receive concurrent chemoradiation therapy after biopsy (n = 929), or died within 2 months of biopsy (n = 95). A total of 3456 patients were included in this initial cohort (Fig. 1).

To investigate the relationship between timing of radiotherapy and survival outcomes, Fig. 2 demonstrates the relationship between the natural logarithm of HR and time to radiotherapy modeled as a continuous variable. These results show that survival remains largely unchanged if radiotherapy is started between approximately 3 and 8 weeks. To further examine this, the Kaplan-Meier curve for patients who received radiotherapy within 3 weeks of biopsy was plotted in comparison with patients who received radiation after 3 weeks in Fig. 3. This figure demonstrates that patients who received radiotherapy within 3 weeks of biopsy had significantly lower survival compared with patients who received radiotherapy after 3 weeks. A forest plot displaying HRs for timing of radiation in data sets in which patients who received radiotherapy 0–3 weeks after biopsy were excluded is shown in Supplemental Fig. 1. These results show that when patients who received radiotherapy within 3 weeks of biopsy were excluded, timing of radiotherapy was not associated with survival.

Because of concerns about unmeasurable confounding factors in patients who received radiotherapy within 3 weeks of biopsy, such as more clinically aggressive disease, these patients were excluded, leaving a final total of 2667 patients. The median time to radiotherapy was 32

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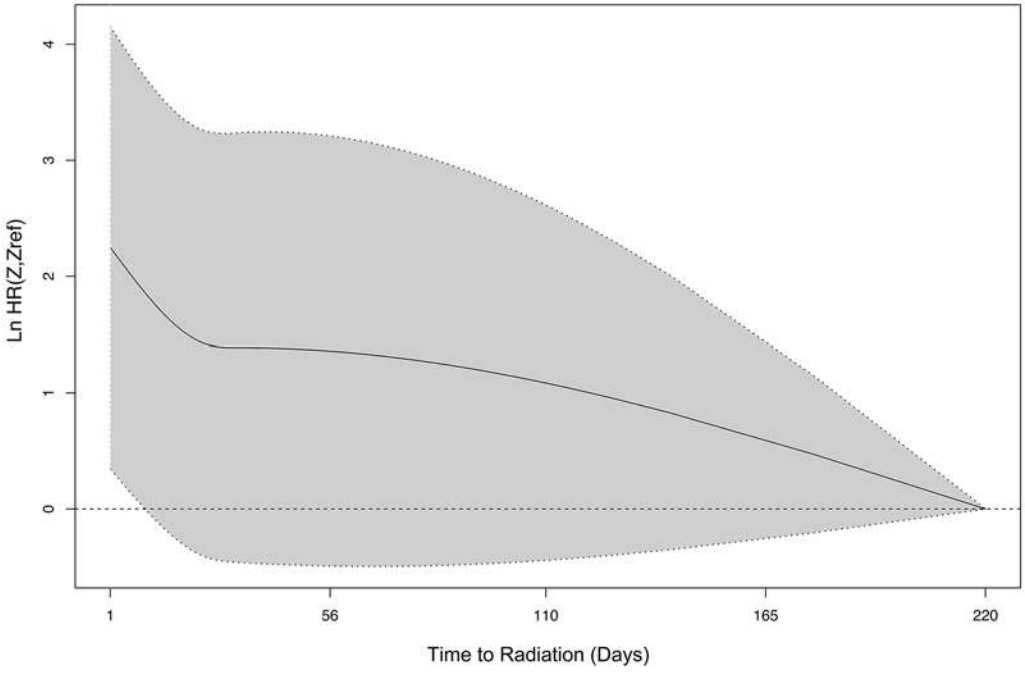

FIG. 2. Natural logarithm of HR along with 95% CI versus time to radiotherapy modeled as a continuous variable (n = 3456).

days (mean 35 days). As such, the cohort was then separated into those who received radiotherapy 3–5 weeks and > 5 weeks after biopsy. Overall, 1782 (66.82%) patients received radiotherapy 3–5 weeks after biopsy and 885 (33.18%) patients received radiotherapy > 5 weeks after biopsy. Compared with those who received radiotherapy 3–5 weeks after biopsy, patients who received radiotherapy > 5 weeks after biopsy were more likely to have lower income (< $63,000) (60.16% vs 64.63%, p = 0.021), to be Black/African American (4.83% vs 8.14%, p = 0.001), and to have no insurance (3.25% vs 5.42%, p < 0.001) (Table 1).

Patients who received radiotherapy 3–5 weeks after biopsy had a median OS of 14.4 months (95% CI 13.6–15.3), and patients who received radiotherapy > 5 weeks had a median OS of 15.0 (95% CI 13.9–16.2; log-rank p = 0.504) (Fig. 4). Multivariable analysis accounting for age, sex, KPS score, MGMT status, facility type, location, and insurance demonstrated that patients who received radiotherapy > 5 weeks after biopsy did not have a significant difference in survival compared with patients who received radiotherapy sooner (HR 0.96, 95% CI 0.88–1.05; p = 0.374 (Table 2). When time to radiotherapy was analyzed as a continuous

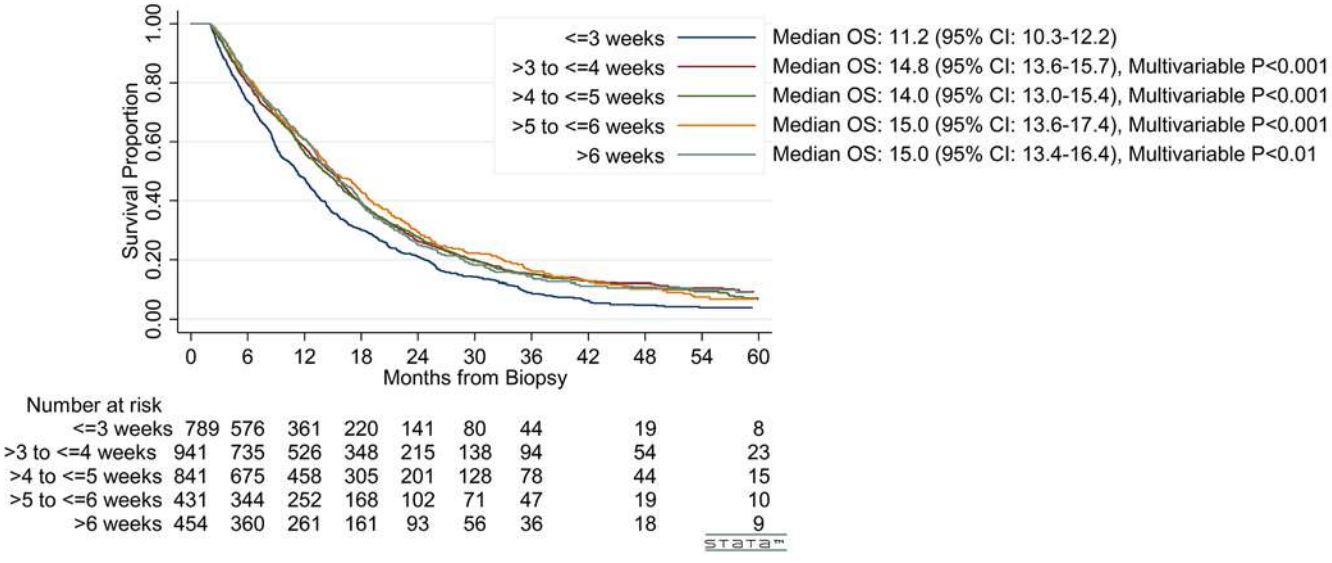

FIG. 3. Kaplan-Meier curve for OS stratified by time interval from biopsy to radiotherapy (with time modeled as a categorical variable split as within 3, 3–4, 4–5, 5–6, and > 6 weeks). Figure is available in color online only.

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TABLE 1. Patient characteristics

Patient Characteristic	Interval From Biopsy to RT 3–5 wks	Interval From Biopsy to RT >5 wks	p Value
No. of patients (%)	1782 (66.82)	885 (33.18)	
Age in yrs, median (IQR)	62 (53–69)	62 (53–69)	0.769
Race, n (%)			0.001
Black/ African American	86 (4.83)	72 (8.14)	
White	1642 (92.14)	777 (87.80)	
Other	43 (2.41)	23 (2.60)	
Unknown	11 (0.62)	13 (1.47)	
Sex, n (%)			0.826
Male	1063 (59.65)	524 (59.21)	
Female	719 (40.35)	361 (40.79)	
KPS score, n (%)			0.165
80–100	167 (9.37)	63 (7.12)	
50–70	67 (3.76)	34 (3.84)	
0–40	12 (0.67)	3 (0.34)	
Unknown	1536 (86.20)	785 (88.70)	
MGMT status, n (%)			0.710
Unmethylated	204 (11.45)	96 (10.85)	
Methylated	135 (7.58)	61 (6.89)	
Unknown	1443 (80.98)	728 (82.26)	
Radiation dose in Gy, median (IQR)	60.00 (59.4–60.0)	60.00 (59.4–60.0)	0.894
Tumor size in cm, median (IQR)	4.7 (3.3–6.4)	5.0 (3.5–7.0)	0.003
Facility type, n (%)			0.837
Academic	875 (49.10)	425 (48.02)	
Nonacademic	652 (36.59)	334 (37.74)	
Unknown	255 (14.31)	126 (14.24)	
Income, n (%)			0.021
≥$63,000	694 (38.95)	300 (33.90)	
<$63,000	1072 (60.16)	572 (64.63)	
Unknown	16 (0.90)	13 (1.47)	
Insurance, n (%)			<0.001
None	58 (3.25)	48 (5.42)	
Private	906 (50.84)	403 (45.54)	
Medicaid	106 (5.95)	81 (9.15)	
Medicare	641 (35.97)	325 (36.72)	
Other government	38 (2.13)	22 (2.49)	
Unknown	33 (1.85)	6 (0.68)	
Residence location, n (%)			0.966
Metro	1400 (78.56)	699 (78.98)	
Nonmetro	311 (17.45)	152 (17.18)	
Unknown	71 (3.98)	34 (3.84)	
Year of diagnosis, n (%)			0.355
2010	402 (22.56)	185 (20.90)	
2011	349 (19.58)	165 (18.64)	
2012	311 (17.45)	174 (19.66)	
2013	356 (19.98)	163 (18.42)	
2014	364 (20.43)	198 (22.37)	
Facility location			<0.001
Northeast	471 (26.43)	267 (30.17)	
South	430 (24.13)	217 (24.52)	
Midwest	435 (24.41)	168 (18.98)	
West	350 (19.64)	174 (19.66)	
Unknown	96 (5.39)	59 (6.67)	

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RT = radiotherapy.

variable, it was also found to not be significantly associated with survival (HR 0.99, 95% CI 0.99–1.00; p = 0.231) (Table 3). Sequential landmark analysis in this group was carried out by excluding patients who died 0–6 months after biopsy. A forest plot showing the results of sequential landmark analysis from 0 to 6 months is shown in Supplemental Fig. 2 and demonstrates that timing of radiotherapy did not significantly influence survival when patients were excluded 0–6 months following biopsy.

A subgroup analysis was conducted in patients who completed radiotherapy at 40.00 Gy in 15 fractions, 40.05 Gy in 15 fractions, or 60.00 Gy in 30 fractions. Again, there was no significant difference in survival between those who received radiotherapy earlier and those who received it later (median OS 15.7 months, 95% CI 14.7–16.3 months vs median OS 16.9 months, 95% CI 15.9–18.0 months; multivariable p = 0.124) (Supplemental Fig. 3).

Consistent with this analysis, timing of radiotherapy was not associated with survival when multiple imputation was implemented for missing data (HR 0.95, 95% CI 0.84–1.06) (Supplemental Table 1).

Discussion

Although the current treatment paradigm for patients with glioblastoma includes maximal safe resection followed by radiotherapy and concurrent temozolomide, approximately 15%–30% of all patients diagnosed with glioblastoma receive a biopsy instead of a debulking resection.[9,10] These biopsy-only patients belong to a particularly vulnerable group, as numerous studies have shown that these patients have worse outcomes compared with those who undergo resection.[10,13] In the pretemozolomide era, a retrospective study of three RTOG (Radiation Therapy Oncology Group) randomized trials showed that in 645 patients with glioblastoma, those who received only a biopsy had a significantly lower median OS (6.6 months) compared with those who received subtotal resection (10.4

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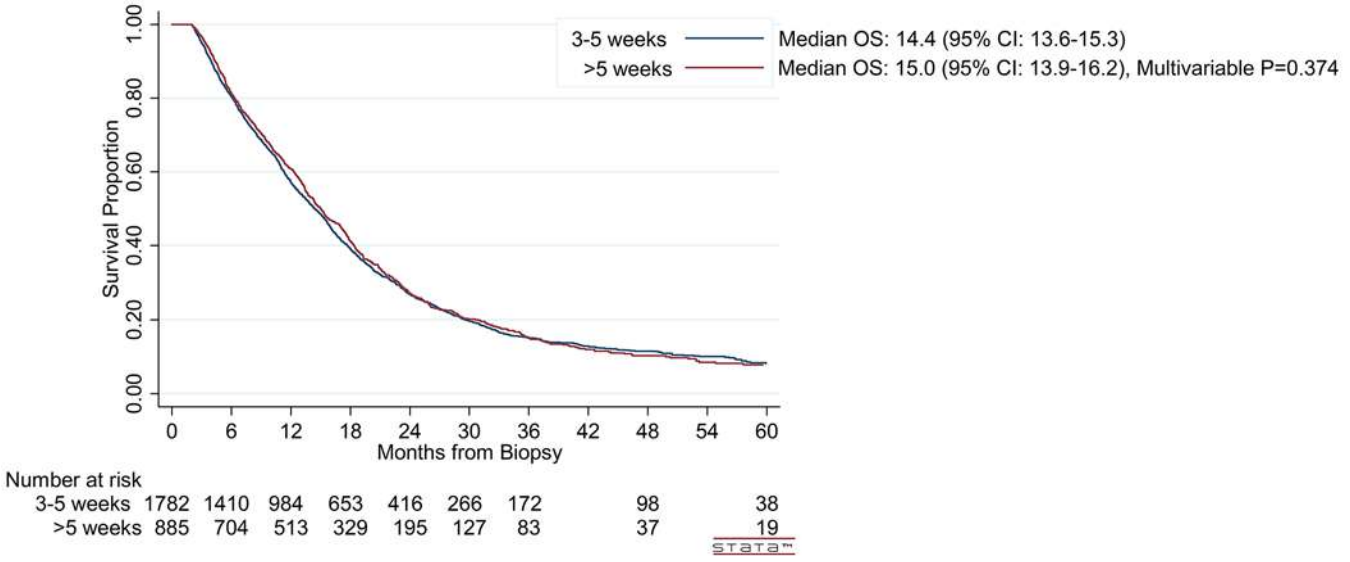

FIG. 4. Kaplan-Meier curve for OS stratified by time interval from biopsy to radiotherapy (with time modeled as a dichotomous variable split as 3–5 weeks and > 5 weeks). Figure is available in color online only.

months) or gross-total resection (11.3 months).[14] In the EORTC-NCIC, the small subset of biopsy-only patients who received radiotherapy and temozolomide had a median OS of only 9.4 months. Compared with the median OS of the entire cohort, which was 14.6 months, biopsy-only patients were again found to have considerably worse survival.[3]

In addition to having poorer survival outcomes, biopsy-only glioblastoma patients are reported to have worse neurological and performance status.[10,14–16] Often, this can be due to tumor location, since one common reason for foregoing debulking surgery is a tumor located in a deep or unfavorable area of the brain (i.e., thalamus). Moreover, without more extensive resection, these patients can continue to have persistent mass effect caused by their tumor and associated edema. Management of these neurological symptoms may require high doses of steroids, particularly during radiotherapy.[10,16] However, few studies have explored how the current management regimen should be tailored for patients who receive biopsy only.

The impact of the timing of radiotherapy in biopsy-only patients on survival outcomes is one such area that remains unclear. Patients who undergo biopsy are commonly advised to begin radiotherapy as soon as safely possible.[17] The predominant reason behind this recommendation is the aggressive nature of glioblastoma, which has a mean tumor volume doubling time of 24 days.[18] However, there may be multiple reasons that could delay radiotherapy initiation, including postponements in molecular testing results regarding isocitrate dehydrogenase (IDH) mutations and MGMT methylation status, complex treatment planning, or the effects of the COVID-19 pandemic on either the patient or the treating radiation oncology department. Our study suggests that in light of these constraints, a slight delay in initiating radiotherapy after biopsy may be acceptable if necessary.

Prior studies examining the timing of radiotherapy in glioma patients who were able to undergo resection have shown similar results. Nathan et al. retrospectively analyzed 2535 high-grade glioma patients who underwent craniotomies as well as adjuvant radiotherapy and temozolomide from the Clinformatics Data Mart database, showing that starting radiotherapy within 4 weeks of surgery was associated with significantly worse survival than delaying radiotherapy past 4 weeks.[17] However, while demographic features such as age, race, and sex were considered, this study may have been affected by selection bias due to a lack of important clinical data such as performance status and MGMT status. Additionally, this study included patients with grade III gliomas, and so the applicability of these results to glioblastoma patients, particularly biopsy-only glioblastoma patients, is questionable.[19]

In contrast, in a retrospective review by Spratt et al. of 345 glioblastoma patients who were treated with adjuvant radiotherapy and temozolomide (among whom only 17.1% underwent a biopsy instead of debulking resection), delaying radiotherapy past 6 weeks after surgery was associated with a decrease in OS on multivariable analysis compared with beginning radiotherapy within 2 weeks of surgery.[20] The majority of other studies on this topic have shown no correlation between interval to radiotherapy and survival.[21–24] Blumenthal et al. utilized data from RTOG 0525 and RTOG 0825 to examine the impact of timing of radiotherapy in 1395 glioblastoma patients, the majority of whom received either a gross-total or subtotal resection.[25] The patient cohort was stratified into those who received radiotherapy within 4 weeks of surgery and after 4 weeks of surgery, and no significant difference in survival was found between the two groups. Of note, generalizability remained a major limitation of this study, as only patients who were eligible for these two clinical trials were included. Finally, a recent retrospective analysis by Press et al. demonstrated that among glioblastoma patients who underwent resection, delaying adjuvant chemotherapy and radiotherapy beyond 5 weeks did not negatively impact outcomes.[26] However, early initiation of adjuvant treat-

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TABLE 2. Cox regression analysis of OS stratified by interval from biopsy to radiation after the exclusion of patients who received radiotherapy within 3 weeks (time modeled as dichotomous variable)

Patient Characteristic	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	p Value	HR	95% CI	p Value
Interval from biopsy to RT, wks						
3–5 (ref)						
>5	0.97	0.89–1.06	0.504	0.96	0.88–1.05	0.374
KPS score						
80–100 (ref)						
50–70	1.83	1.43–2.36	<0.001	1.80	1.40–2.32	<0.001
0–40	1.64	0.96–2.83	0.074	1.74	1.01–3.01	0.048
Unknown	1.15	0.99–1.34	0.065	1.14	0.98–1.33	0.085
Age, yrs	1.03	1.02–1.03	<0.001	1.03	1.02–1.03	<0.001
Tumor size, cm	0.99	0.99–1.00	0.400			
Radiation dose, Gy	0.99	0.99–1.00	0.911			
Race						
White (ref)						
Black	0.85	0.70–1.02	0.079			
Other	0.65	0.48–0.88	0.006			
Sex	0.97	0.60–1.57	0.910			
Male (ref)						
Female	0.89	0.82–0.97	0.009	0.88	0.81–0.96	0.005
Facility type						
Academic (ref)						
Nonacademic	1.18	1.08–1.29	<0.001	1.14	1.04–1.26	0.006
Other	0.85	0.74–0.96	0.011	1.05	0.90–1.23	0.511
Income						
≥$63,000 (ref)						
<$63,000	1.11	1.02–1.21	0.021			
Unknown	1.38	0.92–2.05	0.116			
Insurance						
None (ref)						
Private	1.12	0.89–1.41	0.348	1.18	0.93–1.49	0.164
Medicaid	1.22	0.92–1.61	0.159	1.39	1.05–1.84	0.020
Medicare	1.99	1.58–2.52	<0.001	1.37	1.07–1.76	0.013
Other government	1.56	1.09–2.21	0.013	1.41	0.99–2.00	0.059
Unknown	1.41	0.93–2.13	0.103	1.25	0.83–1.89	0.291
Residence location						
Metro (ref)						
Nonmetro	1.09	0.98–1.22	0.110			
Unknown	0.83	0.66–1.04	0.105			
MGMT status						
Unmethylated (ref)						
Methylated	0.60	0.48–0.73	<0.001	0.55	0.44–0.67	<0.001
Unknown	0.89	0.79–1.02	0.098	0.83	0.71–0.93	0.003
Year of diagnosis						
2010 (ref)						
2011	0.94	0.83–1.06	0.292			
2012	0.94	0.83–1.07	0.343			
2013	0.89	0.78–1.01	0.070			
2014	1.03	0.91–1.18	0.617			

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TABLE 2. Cox regression analysis of OS stratified by interval from biopsy to radiation after the exclusion of patients who received radiotherapy within 3 weeks (time modeled as dichotomous variable)

	Univariable Analysis			Multivariable Analysis		
Patient Characteristic	HR	95% CI	p Value	HR	95% CI	p Value
Location						
Northeast (ref)						
Midwest	1.23	1.09–1.38	0.001	1.21	1.07–1.36	0.002
South	1.20	1.07–1.35	0.002	1.20	1.07–1.36	0.002
West	1.04	0.92–1.18	0.497	1.04	0.91–1.18	0.585
Unknown	0.58	0.47–0.72	<0.001	1.34	0.99–1.81	0.060

ment, defined as chemotherapy and radiotherapy within 3 weeks of surgery, was associated with worsened OS. These results were consistent across recursive partitioning analysis classes, suggesting that selection bias may not be the only explanation for the poorer survival outcomes in patients who received earlier adjuvant treatment. However, the authors also acknowledged that patients with negative clinical factors not accounted for in the database may have been referred for adjuvant treatment earlier.

When examining time to radiotherapy as a continuous variable, we found that later time to radiotherapy was associated with improved survival between 0 and 3 weeks, but there was no significant change in survival between 3 and 8 weeks. This is likely due to the fact that patients who were judged to have more clinically significant disease (possibly more neurologically symptomatic) were selected to begin therapy sooner, and that this was not fully accounted for by factors included in this study, such as KPS score, tumor size, age, or MGMT status. In an effort to reduce unmeasured confounding and account for the possibility that poorer-performing patients were more likely to receive expedited treatment, we excluded patients who received radiotherapy within 3 weeks of surgery.

After excluding patients who died within 3 weeks of biopsy, there was no significant difference in the KPS scores of patients who received radiotherapy within 5 weeks of biopsy compared with those who delayed radiotherapy past 5 weeks. Patients who had delayed radiotherapy had more unfavorable socioeconomic characteristics, such as residing in a lower-income region and greater likelihood of being uninsured or on Medicaid. Therefore, selection bias may be expected to work against patients with later radiotherapy, strengthening our conclusions that delaying radiotherapy may not necessarily lead to a survival detriment. We also performed sensitivity analyses limited to only patients who completed standard dose-fractionation schemes, which we defined as 40.00 Gy in 15 fractions, 40.05 Gy in 15 fractions, or 60.00 Gy in 30 fractions, as well as a sequential landmark analysis. In each of these subset analyses, we found that later radiotherapy was not associated with poorer survival outcomes.

Study Limitations

Several other limitations are inherent to the retrospective nature of our study. The NCDB does not give information on perioperative complications or disease-specific survival, factors that may significantly affect OS. For example, MGMT status was missing for the majority of patients in this study, and IDH mutation status was completely missing. These are major limitations in the molecular era of neuro-oncology where MGMT and IDH status have become increasingly important for the prognostication and treatment of patients with glioblastoma. To address this limitation, we attempted to account for missing data through multiple imputation, but this method can be unreliable in the setting of a large percentage of unknown values. Future research into this topic should consider including MGMT and IDH status, especially since a large portion of prior studies examining the impact of radiotherapy timing on survival in glioblastoma patients lack data on IDH and MGMT status.

Additionally, KPS scores were also unknown for the majority of patients in this study. As such, it is difficult to fully account for performance status as a confounding factor. Patients with poor performance may have disproportionately received early rather than delayed radiotherapy, which would impact our results. Again, we attempted to address this limitation by imputing the missing KPS data, but given the large percentage of unknown values, it is unclear if our results based on imputation are reliable. However, it is reassuring to note that a recent retrospective analysis that accounted for recursive partitioning analysis class found that that delayed radiotherapy did not result in worse outcomes, a result that is consistent with our findings.[26]

The NCDB does not provide information about the radiation field, treatment interruptions, or details of chemotherapy. Lastly, immortal time bias was a limitation in this study since immediate postoperative complications could artificially enhance survival in one patient cohort compared with the other. We accounted for this in primary analysis and sensitivity analyses.

Conclusions

Our study demonstrates that reasonable delays in radiotherapy after biopsy are not associated with inferior survival in patients receiving biopsy only for glioblastoma. While we do not recommend purposefully postponing adjuvant treatment, our data suggest that a delay in radiotherapy to allow for complex radiation treatment planning

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TABLE 3. Cox regression analysis of OS stratified by interval from biopsy to radiation after the exclusion of patients who received radiation within 3 weeks (time modeled as continuous variable)

Patient Characteristic	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	p Value	HR	95% CI	p Value
Interval from biopsy to RT, days	0.99	0.99–1.00	0.203	0.99	0.99–1.00	0.231
KPS score						
80–100 (ref)						
50–70	1.83	1.43–2.36	<0.001	1.81	1.40–2.33	<0.001
0–40	1.64	0.96–2.83	0.074	1.74	1.01–3.01	0.047
Unknown	1.15	0.99–1.34	0.065	1.15	0.98–1.33	0.079
Age, yrs	1.03	1.02–1.03	<0.001	1.03	1.02–1.03	<0.001
Tumor size, cm	0.99	0.99–1.00	0.400			
Radiation dose, Gy	0.99	0.99–1.00	0.911			
Race						
White (ref)						
Black	0.85	0.70–1.02	0.079			
Other	0.65	0.48–0.88	0.006			
Sex	0.97	0.60–1.57	0.910			
Male (ref)						
Female	0.89	0.82–0.97	0.009	0.88	0.81–0.96	0.005
Facility type						
Academic (ref)						
Nonacademic	1.18	1.08–1.29	<0.001	1.14	1.04–1.26	0.006
Other	0.85	0.74–0.96	0.011	1.05	0.90–1.23	0.532
Income						
≥$63,000 (ref)						
<$63,000	1.11	1.02–1.21	0.021			
Unknown	1.38	0.92–2.05	0.116			
Insurance						
None (ref)						
Private	1.12	0.89–1.41	0.348	1.17	0.93–1.48	0.180
Medicaid	1.22	0.92–1.61	0.159	1.39	1.05–1.83	0.022
Medicare	1.99	1.58–2.52	<0.001	1.36	1.06–1.75	0.015
Other government	1.56	1.09–2.21	0.013	1.41	0.99–2.01	0.057
Unknown	1.41	0.93–2.13	0.103	1.24	0.82–1.88	0.308
Residence location						
Metro (ref)						
Nonmetro	1.09	0.98–1.22	0.110			
Unknown	0.83	0.66–1.04	0.105			
MGMT status						
Unmethylated (ref)						
Methylated	0.60	0.48–0.73	<0.001	0.54	0.44–0.67	<0.001
Unknown	0.89	0.79–1.02	0.098	0.82	0.71–0.93	0.003
Year of diagnosis						
2010 (ref)						
2011	0.94	0.83–1.06	0.292			
2012	0.94	0.83–1.07	0.343			
2013	0.89	0.78–1.01	0.070			
2014	1.03	0.91–1.18	0.617			
Location						
Northeast (ref)						

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TABLE 3. Cox regression analysis of OS stratified by interval from biopsy to radiation after the exclusion of patients who received radiation within 3 weeks (time modeled as continuous variable)

Patient Characteristic	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	p Value	HR	95% CI	p Value
Location (*continued*)						
Midwest	1.23	1.09–1.38	0.001	1.21	1.07–1.36	0.002
South	1.20	1.07–1.35	0.002	1.20	1.07–1.36	0.002
West	1.04	0.92–1.18	0.497	1.04	0.91–1.18	0.570
Unknown	0.58	0.47–0.72	<0.001	1.34	0.99–1.82	0.055

or functional improvements may not necessarily have a detrimental effect on survival outcomes.

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Disclosures

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Conception and design: Gao, Park. Acquisition of data: Gao. Analysis and interpretation of data: Gao, Jin, Park. Drafting the article: Gao, Park. Critically revising the article: Gao, Moliterno, Corbin, Bindra, Contessa, Yu, Park. Reviewed submitted version of manuscript: Gao. Approved the final version of the manuscript on behalf of all authors: Gao. Statistical analysis: Gao, Park. Administrative/technical/material support: Gao. Study supervision: Gao, Park.

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