Original Article

Optimal Timing of Chemoradiotherapy After Surgical Resection of Glioblastoma: Stratification by Validated Prognostic Classification

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BACKGROUND: Previous studies examining the time to initiate chemoradiation (CRT) after surgical resection of glioblastoma have been conflicting. To better define the effect that the timing of adjuvant treatment may have on outcomes, the authors examined patients within the National Cancer Database (NCDB) stratified by a validated prognostic classification system. **METHODS:** Patients with glioblastoma in the NCDB who underwent surgery and CRT from 2004 through 2013 were analyzed. Radiation Therapy Oncology Group recursive partitioning analysis (RPA) class (III, IV, V) was extrapolated for the cohort. Time intervals were grouped weekly, with weeks 4 to 5 serving as the reference category for analyses. Kaplan-Meier analysis, log-rank testing, and multivariate (MVA) Cox proportional hazards regression were performed. **RESULTS:** In total, 30,414 patients were included. RPA classes III, IV, and V contained 5250, 20,855, and 4309 patients, respectively. On MVA, no time point after week 5 was associated with a change in overall survival for the entire cohort or for any RPA class subgroup. The periods of weeks 0 to 1 (hazard ratio [HR], 1.18; 95% CI, 1.02-1.36), >1 to 2 (HR, 1.23; 95% CI, 1.16-1.31), and >2 to 3 (HR, 1.11; 95% CI, 1.07-1.15) demonstrated slightly worse overall survival (all $P < .03$). The detriment to early initiation was consistent across each RPA class subgroup. **CONCLUSIONS:** The current data provide insight into the optimal timing of CRT in patients with glioblastoma and describe RPA class-specific outcomes. In general, short delays beyond 5 weeks did not negatively affect outcomes, whereas early initiation before 3 weeks may be detrimental. ***Cancer* 2020;0:1-10**. © *2020 American Cancer Society*.

KEYWORDS: chemoradiotherapy, adjuvant, glioblastoma, radiotherapy, adjuvant, timing of therapy.

INTRODUCTION

Glioblastoma is the most common primary malignant brain tumor, affecting 11,000 patients a year in the United States.[1] Primary treatment is maximally safe resection followed by adjuvant radiation therapy with concurrent and adjuvant chemotherapy.[2] Despite the advance of concurrent adjuvant therapy, outcomes remain dismal, with a median overall survival (OS) of approximately 14 to 16 months. The affected patient population is widely heterogenous, and outcomes vary based on patient, tumor, and treatment factors. For example, performance status, age,[3] extent of resection,[4,5] and *O6-methylguanine-DNA methyltransferase (MGMT)* methylation[6] have demonstrated strong prognostic value.

Within the established standard of care, the time interval from surgery to the start of chemoradiation (CRT) has varied in clinical practice. There are conflicting data defining the optimal timing, and current publications are often limited due to small patient cohorts and confounding factors. Early initiation of adjuvant therapy logically eradicates residual tumor cells before repopulation. This is particularly relevant in an aggressive infiltrative malignancy with a rapid doubling time like glioblastoma.[7] Alternatively, early initiation of adjuvant therapy could be

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The data used in this study are derived from a de-identified National Cancer Database (NCDB) file. The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology used, or the conclusions drawn from these data by the investigator.

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detrimental in the case of incomplete wound healing, postoperative deconditioning,[8] suboptimal tumor reoxygenation,[9] and/or inflammatory changes within the tumor microenvironment.[10]

In this report, we sought to examine the impact of timing in initiating treatment using the National Cancer Database (NCDB). To improve patient stratification and account for confounding clinical factors within the cohort, we applied an extrapolated version of the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) classification system. This is a validated scoring system that stratifies survival based on pretreatment and treatment-related factors derived from 4 historic prospective clinical trials.[11-13] Application of the RPA may help in reducing selection bias and allow for finer discrimination of outcomes based on patient prognosis.

MATERIALS AND METHODS

The NCDB is a national registry administered by the American Cancer Society and the Commission on Cancer of the American College of Surgeons and captures nearly 70% of newly diagnosed malignancies in the United States annually. The database contains detailed patient and treatment characteristics, including demographic information, extent of surgical resection, radiotherapy details, and timing of therapy. Patient data are de-identified; therefore, the current study was granted exempt status by the Emory University Institutional Review Board.

Patients diagnosed with newly diagnosed glioblastoma between 2004 and 2013 were captured from the database. To be included in the study, patients must have undergone a surgical procedure, received adjuvant radiation therapy with concurrent chemotherapy (defined as the initiation of radiation therapy and chemotherapy within 14 days of each other), and received a definitive radiation dose of at least 40 grays (Gy).[14,15] Patients who underwent biopsy were included in this analysis to reflect the RPA criteria. The NCDB identifies whether chemotherapy was received but does not delineate the type or number of cycles of chemotherapy. Patients who died within 8 weeks were excluded to account for immortal time bias. This left 30,414 patients remaining for the current analysis. A Consolidated Standards for Reporting Trials (CONSORT) diagram with inclusion and exclusion criteria is illustrated in Supporting Figure 1.

RPA is a classification system developed from a pooled analysis of 4 RTOG trials that accrued 3052 patients with glioblastoma between 1974 and 2003. The maximum time from surgery to the initiation of adjuvant therapy in those trials was 6 weeks. The classification was initially published in 1993[11] and was simplified in 2011[13] to exclude anaplastic astrocytoma and to include only 4 variables: age, Karnofsky performance status (KPS), extent of resection (total/partial resection vs biopsy), and neurologic status (able to work vs not). RPA class III is defined as all patients aged <50 years with a KPS ≥90. Class IV is defined as patients aged <50 years with a KPS <90 OR those aged ≥50 years with a KPS ≥70, partial/total resection, and functional neurologic status. Class V is defined as aged ≥50 years and either 1) a KPS <70, 2) biopsy only, or 3) poor neurologic function. The final simplified model contained 1672 patients and was confirmed to distinguish OS as well as the original model.[13] The median OS for patients in classes III, IV, and V was 17.1, 11.2, and 7.5 months, respectively.

Within the NCDB, age and extent of resection are included variables. To apply the RPA classification to the NCDB database, KPS and neurologic function were extrapolated from the Charlson-Deyo (CD) score for medical comorbidities. We assigned a CD score of 0 to indicate a KPS of ≥90, a CD score of 1 to indicate a KPS from ≥70 to <90, and a CD score of ≥2 to indicate a KPS <70 and/or poor neurologic function (Fig. 1).

The time from surgery to initiation of adjuvant CRT was divided into weekly categories, (0-1, >1 to 2, >2 to 3, >3 to 4, >4 to 5, >5 to 6, >6 to 7, >7 to 8, and ≥8 weeks). Week >4 to 5 was used as the reference in statistical analysis because it was one of the most common intervals and is our institutional standard goal within which to start adjuvant therapy. Additional variables captured included sex, race, facility type, facility location, median income quartiles, education status, year of diagnosis, primary tumor location, laterality, tumor size (>6 vs ≤6 cm), and radiation dose (≥59 vs <59 Gy). *MGMT* status was collected only in a small percentage of the patient population and thus was not included in the analysis.

Descriptive statistics of patient and treatment characteristics were reported. Associations of these variables to RPA prognostic groups and the time to surgery were compared using the Pearson chi-square test and an analysis of variance for numerical variables, when appropriate. OS was calculated from the date of surgery to the patient's death or last follow-up. Kaplan-Meier curves were generated to assess the univariate associations between OS and patient/treatment characteristics using the log-rank test. Univariate and multivariate Cox proportional hazards regression models were performed for OS. Each variable that had a P value <.1 was included in the

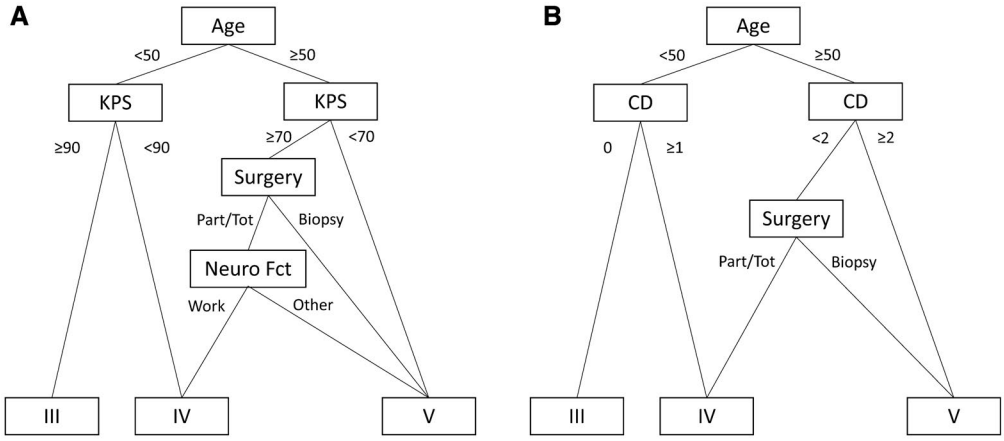


Figure 1. Tree diagrams illustrate (A) the simplified recursive partitioning analysis (RPA) model and (B) the applied RPA model used for the current study. CD indicates Charlson-Deyo comorbidity score; KPS, Karnofsky performance status; Neuro Fct, neurological function; Part/Tot, partial/total resection.

multivariate model. All analyses were performed using SAS 9.4 (SAS Institute, Inc) and SAS macros developed by the Biostatistics and Bioinformatics and Winship Research Informatics Shared Resources at Winship Cancer Institute in Atlanta, Georgia.[16]

RESULTS

Patient Characteristics

There were 30,414 patients with glioblastoma who were included in the analysis. Patient and treatment characteristics are listed in Table 1. Overall, the median age (± SD) at diagnosis was 60 ± 12.9 years, and 59.6% of patients were men. The majority of patients had a CD score of 0 (76.7%). The median time to initiate adjuvant therapy was 28 ± 15.8 days. Differences in baseline characteristics stratified by 3-week intervals are listed in Supporting Table 1.

RPA Class

RPA class III, IV, and V represented 5250 (17.3%), 20,855 (68.6%), and 4309 (14.2%) patients, respectively. Biopsy was performed in 2870 patients (9.4%). By definition, the 3 RPA classes had disparate proportions of patients undergoing biopsy versus total/partial resection as well as different distributions of CD scores. Patients in RPA class III were more likely to be men, nonwhite race, from the West region, from a community program, to have tumor sizes >6 cm, and to receive radiation doses ≥59 Gy ($P < .01$). Patients in RPA class IV (22.4%) and V (23.4%) included slightly greater proportions of patients who received adjuvant therapy within 0 to 3 weeks of surgery compared with those in RPA class III (21.4%; $P < .01$).

Overall Survival

As expected, the median OS was significantly different between RPA class III (20.4 months), RPA class IV (14.2 months), and RPA class V (12.1 months). On univariate analysis, RPA class V (hazard ratio [HR], 2.07; 95% CI, 1.98-2.16) and class IV (HR, 1.75; 95% CI, 1.69-1.81) were associated with worse OS compared with RPA class III ($P < .001$). For the entire cohort, initiation of adjuvant therapy during weeks 0 to 1 (HR, 1.24; 95% CI, 1.08-1.43), weeks >1 to 2 (HR, 1.3; 95% CI, 1.22-1.38), weeks >2 to 3 (HR, 1.14; 95% CI, 1.1-1.19), and weeks >3 to 4 (HR, 1.04; 95% CI, 1.00-1.07) was associated with worse OS compared with initiation during week >4 to 5. No differences were seen for any time point >5 weeks. Other factors negatively associated with OS included age ≥50 years, biopsy only, higher CD score, male gender, treatment at a community program, location in the Midwest and South, lower median income quartile, lower percentage of high school degree quartile, higher CD score, early year of diagnosis, primary site, bilateral brain involvement, and radiation dose <59 Gy. West location and nonwhite race were positively associated with OS.

On multivariate analysis (Table 2), the initiation of adjuvant therapy at week 0 to 1 (HR, 1.18; 95% CI, 1.02-1.35), weeks >1 to 2 (HR, 1.23; 95% CI, 1.16-1.31), and weeks >2 to 3 (HR, 1.11; 95% CI, 1.06-1.15) remained associated with worse OS. No significant associations with OS were present at any time point >5 weeks. RPA class IV (HR, 1.73; 95% CI, 1.67-1.8) and class V (HR, 2.11; 95% CI, 2.01-2.21) remained associated with worse OS compared with class III ($P < .001$). In addition, male gender, race, facility location, facility type, income, year

TABLE 1. Patient and Treatment Characteristics, N = 30,414

Variable	No. of Patients (%)
Weeks from surgery to CRT	
0-1	225 (0.7)
>1-2	1355 (4.5)
>2-3	5228 (17.2)
>3-4	8422 (27.7)
>4-5	7389 (24.3)
>5-6	3808 (12.5)
>6-7	1758 (5.8)
>7-8	862 (2.8)
>8	1367 (4.5)
RPA class	
III	5250 (17.3)
IV	20,855 (68.6)
V	4309 (14.2)
Age: Median ± SD, y	60 ± 12.9
≥50	24,258 (79.8)
<50	6156 (20.2)
Sex	
Men	18,139 (59.6)
Women	12,275 (40.4)
Race	
White	18,139 (91.5)
Black	1532 (5.0)
Other/unknown	1061 (3.5)
Charlson-Deyo score	
0	23,328 (76.7)
1	4521 (14.9)
2	2565 (8.4)
Year of diagnosis	
2004-2005	4477 (14.7)
2006-2007	5487 (18.0)
2008-2009	6029 (19.8)
2010-2011	6828 (22.5)
2012-2013	7593 (25.0)
Median income quartile	
<$38,000	3993 (13.1)
$38,000-$47,999	6625 (21.8)
$48,000-$62,999	8325 (27.4)
>$63,000	10,687 (35.1)
Unknown	784 (2.6)
Primary site	
Frontal/temporal lobe	16,966 (55.8)
Occipital/parietal lobe	6574 (21.6)
Other/ventricle/cerebellum	6874 (22.6)
Laterality	
Unilateral	30,190 (99.26)
Bilateral/midline	224 (0.74)
Facility type	
Community	14,395 (47.3)
Academic	12,869 (42.3)
Other	3150 (10.4)
Facility location	
Northeast	6216 (20.4)
South	9097 (29.9)
Midwest	7960 (26.2)
West	7141 (23.5)
Tumor size: Median ± SD, cm	4.5 ± 6.1
>6	3870 (12.7)
≤6	21,076 (69.3)
Unknown	5468 (18.0)
Extent of resection	
Partial/gross total resection	27,544 (90.6)
Biopsy	2870 (9.4)
Radiation dose: Median ± SD, Gy	60 ± 3.4
≥59	26,884 (88.4)
<59	3530 (11.6)

Abbreviations: CRT, chemoradiation; Gy, grays; RPA, recursive partitioning analysis.

TABLE 2. Multivariate Analysis for Overall Survival

Variable	HR (95% CI)	*P*
Weeks from surgery to CRT		
0-1	1.18 (1.02-1.35)	.022[a]
>1-2	1.23 (1.16-1.31)	<.001[a]
>2-3	1.11 (1.06-1.15)	<.001[a]
>3-4	1.03 (0.99-1.06)	.142
>4-5	Ref	—
>5-6	1.02 (0.98-1.06)	.408
>6-7	1.00 (0.94-1.06)	.937
>7-8	1.04 (0.96-1.12)	.317
>8	0.96 (0.90-1.03)	.243
RPA class		
III	2.11 (2.01-2.21)	<.001[a]
IV	1.73 (1.67-1.80)	<.001[a]
V	Ref	—
Sex		
Men	1.11 (1.08-1.14)	<.001[a]
Women	Ref	—
Race		
White	0.85 (0.80-0.90)	<.001[a]
Black	0.77 (0.72-0.83)	<.001[a]
Other/unknown	Ref	—
Year of diagnosis		
2004-2005	1.04 (1.00-1.09)	.034
2006-2007	1.05 (1.01-1.09)	.008
2008-2009	Ref	—
2010-2011	0.95 (0.92-0.99)	.007
2012-2013	0.93 (0.89-0.96)	<.001
Median income quartile		
<$38,000	1.13 (1.08-1.18)	<.001[a]
$38,000-$47,999	1.13 (1.09-1.16)	<.001[a]
$48,000-$62,999	1.07 (1.03-1.10)	<.001[a]
>$63,000	Ref	—
Unknown	1.52 (1.41-1.63)	<.001[a]
Primary site		
Frontal/temporal lobe	Ref	—
Occipital/parietal lobe	1.03 (1.00-1.06)	.096
Other/ventricle/cerebellum	1.27 (1.17-1.39)	<.001[a]
Laterality		
Unilateral	Ref	—
Bilateral/midline	1.48 (1.22-1.79)	<.001[a]
Facility type		
Community	1.10 (1.07-1.13)	<.001[a]
Academic	Ref	—
Other	1.10 (1.05-1.14)	<.001[a]
Facility location		
Northeast	Ref	—
South	1.06 (1.02-1.10)	.001[a]
Midwest	1.07 (1.03-1.11)	<.001[a]
West	0.93 (0.90-0.97)	<.001[a]
Tumor size, cm		
>6	1.07 (1.03-1.11)	<.001[a]
≤6	Ref	—
Unknown	1.00 (0.97-1.03)	.988
Radiation dose, Gy		
≥59	Ref	—
<59	1.52 (1.46-1.57)	<.001[a]

Abbreviations: CRT, chemoradiation; Gy, grays; HR, hazard ratio; Ref, reference category; RPA, recursive partitioning analysis.
[a]*P* values indicate significance.

of diagnosis, tumor location, bilateral tumor involvement, tumor size, and radiation dose all had an effect on OS.

When evaluating each RPA class as individual cohorts, the early initiation of adjuvant therapy remained

TABLE 3. Multivariate Analyses on the Effect of Time From Surgery to Chemoradiation on Overall Survival by Recursive Partitioning Analysis Class

Weeks From Surgery to CRT	HR (95% CI)	*P*
RPA class III		
0-1	1.06 (0.74-1.52)	.741
>1-2	1.36 (1.16-1.59)	<.001[a]
>2-3	1.16 (1.05-1.28)	.003[a]
>3-4	1.09 (1.00-1.18)	.060
>4-5	Ref	—
>5-6	1.04 (0.93-1.17)	.465
>6-7	0.97 (0.84-1.13)	.709
>7-8	0.97 (0.80-1.17)	.730
>8	0.99 (0.86-1.15)	.946
RPA class IV		
0-1	1.04 (0.88-1.24)	.647
>1-2	1.19 (1.10-1.28)	<.001[a]
>2-3	1.08 (1.04-1.14)	<.001[a]
>3-4	1.01 (0.97-1.05)	.685
>4-5	Ref	—
>5-6	1.02 (0.97-1.08)	.385
>6-7	1.02 (0.95-1.09)	.545
>7-8	1.04 (0.95-1.14)	.410
>8	0.96 (0.89-1.04)	.342
RPA class V		
0-1	2.15 (1.55-2.98)	
>1-2	1.37 (1.17-1.60)	<.001[a]
>2-3	1.15 (1.04-1.27)	.008[a]
>3-4	1.04 (0.95-1.14)	.393
>4-5	Ref	—
>5-6	0.98 (0.87-1.10)	.707
>6-7	0.94 (0.81-1.09)	.393
>7-8	1.12 (0.92-1.37)	.249
>8	0.93 (0.78-1.10)	.388

Abbreviations: CRT, chemoradiation; HR, hazard ratio; Ref, reference category; RPA, recursive partitioning analysis.
[a]*P* values indicate significance.

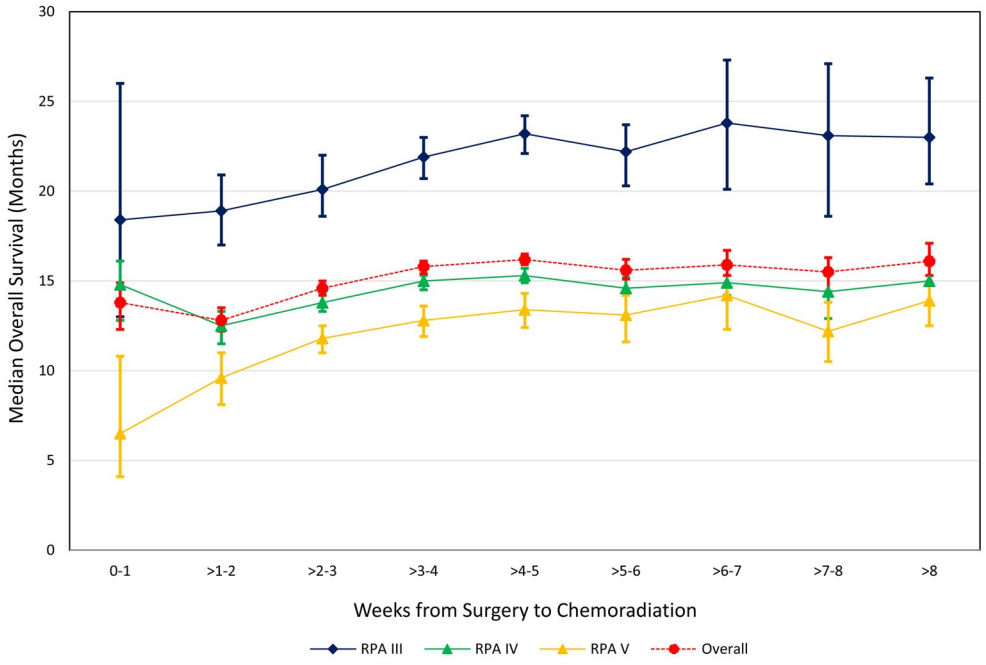
associated with worse OS on multivariate analysis (Table 3). RPA class III demonstrated worse OS for weeks >1 to 2 (HR, 1.36; 95% CI, 1.16-1.59) and weeks >2 to 3 (HR, 1.16; 95% CI, 1.05-1.28). RPA class IV demonstrated worse OS for weeks >1 to 2 (HR, 1.19; 95% CI, 1.10-1.28) and weeks >2 to 3 (HR, 1.04; 95% CI, 1.04-1.14). RPA class V demonstrated worse OS for weeks 0 to 1 (HR, 2.15; 95% CI, 1.55-2.98), >1 to 2 (HR, 1.37; 95% CI, 1.17-1.6), and weeks >2 to 3 (HR, 1.15; 95% CI, 1.04-1.27; $P < .01$). Similar to the general cohort, there were no differences in OS for any time point >5 weeks (Table 3). Other significant variables are listed in Supporting Table 2. Depictions of the median OS per week interval for each RPA class and for the overall cohort are provided in Figure 2. Of note, patients within RPA class V who had a poor performance status and underwent partial/gross total resection demonstrated worse OS than those who underwent biopsy alone (HR, 0.87; 95% CI, 0.82-0.93; $P < .001$). Kaplan-Meier curves per week interval for the entire cohort and for each RPA class are displayed in Figures 3 and 4, respectively.

DISCUSSION

Our study demonstrated no significant detriment in OS with delayed initiation of adjuvant therapy up to 8 weeks compared with 4 to 5 weeks. This finding was consistent across the entire cohort as well as within each RPA class. The absence of an effect on survival with a prolonged time interval suggests that a short delay in the initiation of CRT beyond the traditional 4 to 5 weeks may not negatively affect OS in patients with glioblastoma and should be considered if clinically indicated without undue concern. Conversely, the current study also demonstrated a modest detriment in OS with early initiation of adjuvant therapy, defined as within 3 weeks from surgery (HR ranging from 1.11 to 1.23). Although this finding may be heavily influenced by selection bias, the detrimental effect persisted across each RPA class, suggesting that it cannot be attributed entirely to patients with a poor prognosis.

Given the range of prognostic factors in glioblastoma, the overall impact of differential timing of adjuvant therapy may vary based on patient selection. The goal of this study was to account for these possible confounders by extrapolating the validated RPA classification system to the NCDB cohort. Importantly, our applied RPA system successfully stratified OS, serving as internal validation. The median OS for RPA class III, IV, and V was 20.4, 14.2, and 12.1 months, respectively ($P < .001$). These outcomes are comparable to the Eastern Organization for Research and Treatment of Cancer (EORTC) validation study of the RPA classification after adjuvant CRT, which reported a median OS of 17, 15, and 10 months for RPA class III, IV, and V, respectively.[12] Our applied RPA also had similar proportions of the population classified as class III, IV, and V compared with the EORTC study. Class III, IV, and V in the current study represented 17.3%, 68.6%, and 14.2% of patients, respectively, whereas, in the EORTC study, the same classes represented 15%, 53%, and 32% of patients, respectively. The variation between patients in RPA class IV and V may be attributed to the potential reclassification of patients with poor neurologic function as well as the dose exclusion criteria. Overall, the applied RPA successfully stratifies OS within the NCDB population and recapitulates the general proportions of patients consistent with what was reported in previous large trials.

Multiple studies have similarly demonstrated either no detriment[17-21] or even a modest OS benefit from delayed therapy after accounting for other clinical factors.[22-26] Perhaps the strongest evidence to date is from a meta-analysis by Loureiro et al, who examined



Median Overall Survival per Week Interval from Surgery to Chemoradiation (Months)									
	0-1	>1-2	>2-3	>3-4	>4-5	>5-6	>6-7	>7-8	>8
RPA III	18.4	18.9	20.1	21.9	23.2	22.2	23.8	23.1	23.0
RPA IV	14.8	12.5	13.8	15.0	15.3	14.6	14.9	14.4	15.0
RPA V	6.5	9.6	11.8	12.8	13.4	13.1	14.2	12.2	13.9
Overall	13.8	12.8	14.6	15.8	16.2	15.6	15.9	15.5	16.1

Figure 2. Median overall survival, with 95% confidence intervals (error bars), per week interval is illustrated for each recursive partitioning analysis (RPA) class and for all patients in the overall cohort.

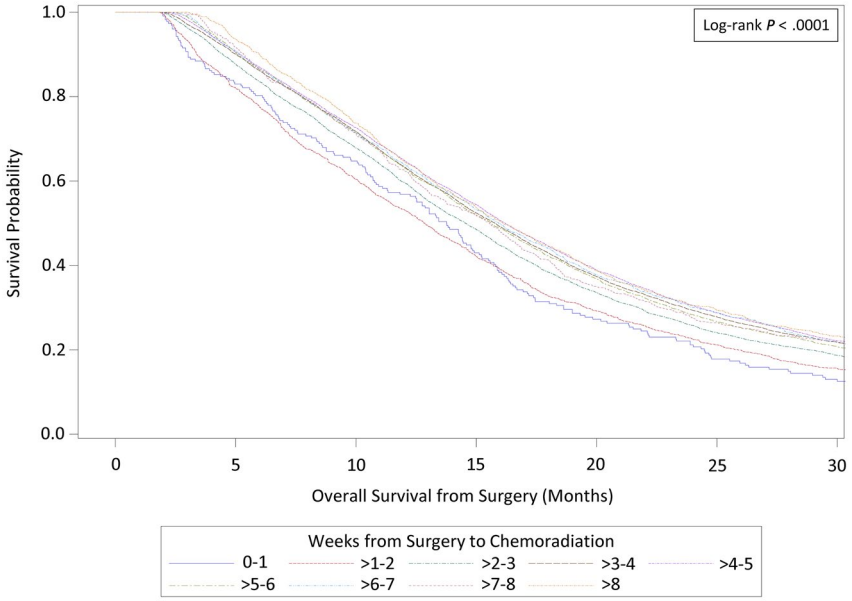


Figure 3. Kaplan Meier curves demonstrate overall survival per week interval for all patients. RPA indicates recursive partitioning analysis; Surg, surgery.

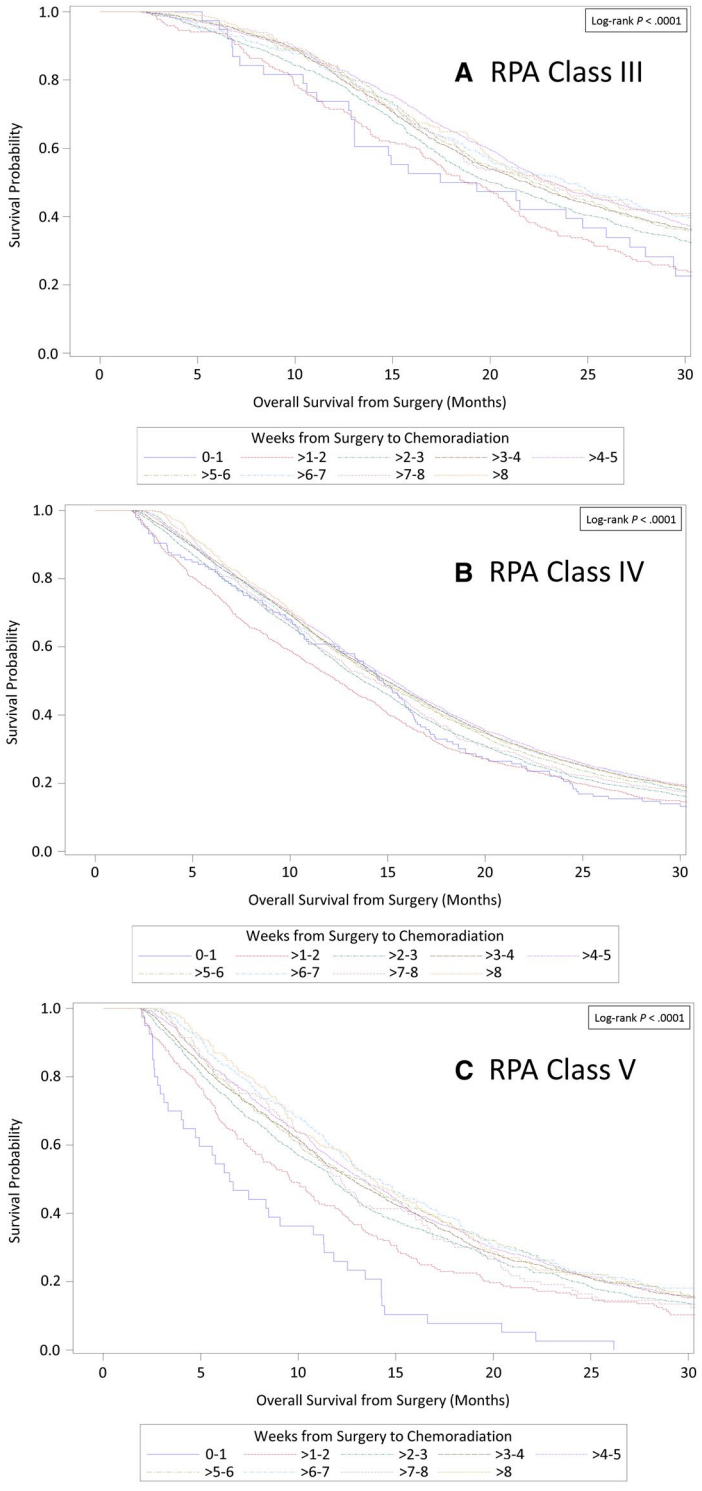


Figure 4. Kaplan Meier curves demonstrate overall survival per week interval for recursive partitioning analysis (RPA) (A) class III, (B) class IV, and (C) class V. Surg indicates surgery.

12 retrospective studies that included a total of 5212 patients. Overall, no effect was identified based on differential wait times (HR, 0.98; 95% CI, 0.9-1.08), and this result persisted after meta-regression weighting for other prognostic factors. The authors concluded that there was no evidence of an effect on survival in delaying

radiotherapy for patients with glioblastoma.[17] There also have been several reports of an initial positive effect on univariate analysis but, ultimately, no effect in the final multivariate model.[18,19,21] This trend emphasizes the need to account for known prognostic factors when evaluating this variable.

The only studies to examine the time interval of adjuvant therapy stratified by RPA classification subgroups were both secondary analyses of pooled, prospective RTOG trials by Blumenthal et al.[22,24] The first study evaluated 4 historic RTOG trials using adjuvant radiation therapy alone. The overall conclusion of that study identified a small OS advantage with later initiation at >4 to 6 weeks compared with <2 weeks (HR, 0.84; $P < .001$), but there was no difference compared with other time intervals. When broken down by RPA classification, the class V subgroup demonstrated the strongest effect on OS based on time interval.[24] Overall, our results are concordant with those from the Blumenthal et al study, supporting no clear difference in survival with delayed initiation but a possible detriment with early initiation. Our study was also consistent in demonstrating that early initiation had the strongest negative impact on patients who had the worst prognosis. Specifically, the RPA class V subgroup had worse survival in weeks 0 and 1 (HR, 2.15), weeks >1 and 2 (HR, 1.37), and weeks >2 and 3 (HR, 1.15) compared with only weeks >1 and 2 and weeks >2 and 3 for the RPA class III and IV subgroups. The second study by Blumenthal et al was a similar analysis of 2 contemporary RTOG studies using CRT: RTOG 0525 and RTOG 0825. That publication did not identify any difference between ≤4 weeks versus >4 weeks (HR, 0.96; $P = .52$) for the entire cohort, and the results were similar across RPA class subgroups. These findings again compare well with our results demonstrating no significant difference in survival beyond >4 to 5 weeks and no change in effect across the RPA subgroups. A major advantage of our study compared with the studies by Blumenthal et al is the large size of our patient cohort, which allowed for more granular time interval evaluations. Of note, an important caveat to the studies by Blumenthal and colleagues is that they both excluded patients who started therapy after 6 weeks, according to RTOG protocol; therefore, any comparisons must be interpreted in this context.

Conversely, several studies have reported conflicting results, including an OS detriment to delay[27,28] or a detriment in a specific subset of patients.[29,30] For example, a single-institution, retrospective review by Irwin et al reported an 8.9% (95% CI, 2.0%-16.1%) increased risk of death per additional week from surgery to radiotherapy.[28] That study should be compared with the current study using caution because the patient numbers were small, nearly two-thirds received <60 Gy, chemotherapy was not used, and World Health Organization (WHO) grade 3 glioma was included. Another study by Do et al also studied patients with WHO grade 3 and 4 tumors and reported worse OS based on a delay in the time from initial clinical presentation to the initiation of radiotherapy, but they reported no OS detriment based on the time from surgery to radiotherapy.[27] This finding supports our results and suggests that clinical delays from the time of presentation to surgery may have a greater effect on a patient's ultimate prognosis than the time interval between surgery and adjuvant therapy. Sun et al examined The Cancer Genome Atlas (TCGA) database and overall did not identify an effect of delays either beyond a median of 27 days (HR, 1.135; $P = .595$) or when comparing the earliest time interval of <20 days versus ≥36 days ($P = .124$). However, the subset of patients who initiated therapy after ≥42 days (including up to 16 weeks) had worse OS compared with those who initiated therapy <42 days (HR, 1.836; $P = .019$).[29] Again, although the current results did not identify a difference after 6 weeks, extensive delays beyond 6 weeks more likely could be affected by selection bias and should be interpreted with caution.

The current study also identified an OS detriment to early initiation. This finding is consistent with the prior studies that identified a survival advantage to delayed timing when accounting for the different reference periods used in statistical analysis. However, it is important to acknowledge that patients who initiate therapy earlier may have received expedited treatment because of the presence of negative clinical factors.[19,23] Because the RPA classification was derived by accounting for a wide range of clinical factors and was validated to stratify OS, we have worked to minimize these known confounders. Thus our data demonstrating worse outcomes with early adjuvant therapy, even in the best prognostic group, suggest that there may be negative consequences of early adjuvant therapy independent of prognostic stage.

Several hypotheses can be made in an attempt to explain a survival detriment to the early initiation of adjuvant therapy, including postoperative hypoxia and disrupted vasculature from the healing surgical bed, which may reduce radiosensitivity[8,9] or increase radiation-related normal tissue brain injury.[10] Recently, postoperative ischemia has been correlated with worse OS and increased tumor regrowth.[31,32] However, the timing with which postoperative ischemia resolves and its ultimate impact on tumor control is unknown and warrants further investigation.

Overall, this study, in conjunction with a wide range of other publications, suggests that there is no clear detriment with moderately longer wait times. Although the initiation of CRT after 4 to 5 weeks is an intuitively uncomfortable proposition, these data seem to suggest that the poor prognosis of glioblastoma and the inherent radioresistance of the disease may have greater effect on a patient's ultimate mortality than the wait time. Treatment beyond 6 weeks is less clear given the discrepancy in favor[18,20] and against[29,33] extended delays. Although our current results support a finding of no detriment, we do not consider this to be an endorsement of extended treatment intervals if not clinically indicated because the later time periods in these studies contain smaller patient numbers and may be more susceptible to patient selection bias. Our study also could not account for local control, which, if affected, would have implications on the need for salvage therapies and overall patient quality of life.

Interestingly, the majority of studies demonstrating a detriment to treatment delays included significant proportions of patients with grade 3 glioma. This observation suggests that delays may have a greater effect on patients with more radiosensitive disease. Similarly, this theory may be relevant for patients with *MGMT*-methylated glioblastoma. In a single institution study, Spratt et al reported no effect on OS with increasing wait times in the overall population but identified an OS detriment when *MGMT* status was incorporated into the multivariate model.[30] A major limitation of the current study is the small number of patients in the NCDB with known *MGMT* status, which precluded further analysis. Based on the strong prognostic implications of this molecular signature and the greater anticipated response to CRT,[6] the timing of adjuvant therapy in this subset may be more influential and/or may represent another confounding variable. Future models should attempt to incorporate *MGMT* status when possible.

Other limitations include all inherent biases present in a large database study. In addition, the NCDB lacks data on progression-free survival and local control endpoints, which, as previously mentioned, remain clinically relevant because of the need for salvage therapies. It is important to note that the applied RPA classification used in this study is an extrapolation from the original definition, and the association between performance status and CD scores/neurologic function has not been previously validated. Although ultimately the applied RPA classification appropriately stratified patient survival, any conclusions must be interpreted within this context. In addition, patients receiving highly abbreviated courses (<40 Gy) of radiation and/or those receiving radiation alone were excluded from this study, meaning these conclusions should not be extrapolated to patients who are deemed too ill to pursue definitive CRT. Finally, the exact extent of resection is not discernable from the NCDB nor is it included within the RPA classification, despite having known prognostic value.[4]

In conclusion, the current study demonstrates no clear survival detriment with delays beyond 5 weeks from surgery. In addition, the results indicate that there may be an OS detriment with the initiation of adjuvant therapy before 3 weeks from surgery. These results persisted across the RPA classes, supporting that these outcomes are not driven solely by selection bias of patients with disparate prognoses. It is likely that these findings are multifactorial and may include possible effects on tumor control, treatment toxicity, and/or clinical selection bias. This study is not advocating for delaying treatment as a new standard of care. However, these data, taken in the context of other supporting literature, favor avoiding the initiation of adjuvant therapy within the first 3 weeks after surgery if possible and could be used to reassure patients and providers in the scenario of unexpected delays, such as with postoperative complications or the wait times for molecular biomarker testing needed for clinical trial enrollment and other clinical decision making.

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CONFLICT OF INTEREST DISCLOSURES

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