Survival impact of prolonged postoperative radiation therapy for patients with glioblastoma treated with combined-modality therapy

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Abstract

Background. Though conventionally fractionated chemoradiation (CRT) is well tolerated by selected patients with newly diagnosed glioblastoma (GBM), adverse health-related and nonhealth-related factors can lead to unplanned interruptions in treatment. The effects of prolonged time to completion (TTC) of radiation therapy (RT) on overall survival (OS) for these patients are unclear.

Methods. The National Cancer Database (NCDB) was queried for all adult patients with newly diagnosed GBM undergoing surgical resection followed by adjuvant CRT with conventionally fractionated RT (6000–6600 cGy in 30–33 fractions) from 2005 to 2012. TTC was defined as the interval from first to last fraction of RT. Recursive partitioning analysis (RPA) was used to determine a threshold for TTC of adjuvant RT. Cox proportional hazards modeling was used to identify covariates associated with OS.

Results. A total of 13489 patients were included in our cohort. Patients who completed adjuvant RT within the RPA-defined threshold of 46 days from initiation of RT (median OS: 14.0 months, 95% confidence interval (CI) 13.7 to 14.3 months) had significantly improved OS compared to patients with TTC of 47 days or greater (median OS: 12.0 months, 95% CI 11.4 to 12.6 months, $P < .001$). Delays in completing adjuvant RT were relatively common, with 15.0% of patients in our cohort having a TTC of RT of 47 days or greater.

Conclusions. Delays in completing adjuvant RT were associated with a worse survival outcome. Any unnecessary delays in completing adjuvant RT should be minimized while ensuring the safe delivery of therapy.

Key words

glioblastoma | treatment interruptions | time to completion | treatment time | prolonged radiotherapy

Adjuvant chemoradiation (CRT) after maximal safe resection is an established standard of care for patients with newly diagnosed glioblastoma (GBM).¹ While this treatment is generally well tolerated, some patients can experience treatment-related toxicities or develop intercurrent illness,² which may result in unplanned interruptions of radiation therapy (RT).³ Nonhealth-related patient and

logistic factors may also prolong time to completion (TTC) of RT for these patients.^{1,3,4}

Breaks prolonging RT completion have been associated with worsened outcomes in patients with non-small cell lung carcinoma^{5–7} (NSCLC), uterine cervical carcinoma,⁸ and head and neck carcinoma.^{9,10} The effects of protracted adjuvant RT on survival for patients with GBM, however,

have not been well defined.³ Consequently, determining whether interruptions in adjuvant RT affect survival for patients with GBM would be of high clinical significance.

We conducted an analysis using a national database to characterize the effects of prolonged TTC of adjuvant RT on survival for adult patients with newly diagnosed GBM treated with conventionally fractionated postoperative CRT. We sought to determine whether delays prolonging time to completion of adjuvant RT were detrimental to survival for these patients.

Materials and Methods

Database

We performed an analysis using the National Cancer Database (NCDB), a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. As a large, prospectively maintained database, the NCDB collects hospital-level data from more than 1500 CoC-accredited centers, encompassing an estimated 70% of all malignancies diagnosed in the United States.¹¹ The data used in this study are derived from a de-identified NCDB file. The American College of Surgeons and the CoC have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigators.

Cohort Selection

We queried the NCDB for all adult patients with newly diagnosed GBM from 2005 to 2012. Patients with GBM were identified using International Classification of Diseases for Oncology site codes (C700, C710-C719). Patients who did not undergo surgical resection and were biopsied only were excluded from this analysis (Fig. 1). Patients who received biopsy alone were excluded as patient- and tumor-related factors limiting surgical resection including performance status, anatomic location, and multifocal disease extent were not available in the dataset and could not be controlled for in the performed analyses. Patients who did not receive adjuvant RT and chemotherapy (CT) were also excluded. Doses of RT less than 6000 centigray (cGy) or delivered in fewer than 30 fractions were additional exclusion criteria as we restricted our cohort to patients receiving conventionally fractionated adjuvant RT modeled on the RT schedule established by Stupp and colleagues.¹ We included patients receiving up to 6600 cGy and 33 fractions to account for clinicians adding fractions of RT for patients with unplanned treatment interruptions, while maintaining a dose per fraction of approximately 200 cGy.³

Further exclusion criteria included unknown time to initiation (TTI) or completion of adjuvant RT, TTI > 180 days, and TTC < 40 or > 90 days. TTI was defined as the interval from surgical resection to first fraction of adjuvant RT delivered. TTC was defined as the interval from the first to last fraction of adjuvant RT delivered. Forty days was determined to be the minimum time interval in which a patient could complete conventionally fractionated adjuvant RT to a dose of 6000 cGy (starting treatment on a Monday, treated

5 days a week for 6 weeks, with no holidays or unplanned treatment interruptions).

Statistical Analysis

Overall survival (OS) was defined as the interval from last fraction of adjuvant RT until death or censoring. Two separate recursive partitioning analyses (RPAs) were constructed to define a TTC interval associated with the greatest difference in OS using exponential scaling with a single split.¹² The initial model analyzed the full dataset to define an optimal threshold, associated with the greatest difference in OS, for TTC with respect to influence on OS. The defined threshold was then validated by creating 1000 training data sets consisting of a randomly generated sample of 50% of the data and 1000 validation datasets created using the remaining patients. RPA models were fit to each training data set, and optimal TTC thresholds under the validation datasets were summarized. The distribution of cut-points considered in the RPA model and the respective hazard ratios (HRs) for OS associated with each cut-point were also considered (Supplementary Figure 1). The threshold defined for TTC using the RPA models was subsequently used to define intervals for TTC categorization. To consider whether any additional risk was present for patients with greatly delayed TTC, an additional category was defined by splitting 1 week after the RPA-chosen threshold.

Relevant patient and treatment covariates including binned age categories, Charlson/Deyo comorbidity scores, sex, race, facility type, and diagnosis year were extracted from the database and adjusted for in the performed analyses. TTI of adjuvant RT was also included as a covariate, with categorization for TTI intervals determined a priori for patients initiating RT within 3 weeks, during the fourth to sixth week or more than 6 weeks after surgical resection. These intervals for TTI were chosen to facilitate interpretation by using potentially clinical relevant endpoints. In addition to prior work suggesting short delays in TTI may be associated with improved outcomes,¹³ previous data suggest potential associations with negative prognostic factors and patients initiating RT within 21 days of surgical resection.^{14,15} Patients initiating RT more than 6 weeks from resection additionally were excluded from 16 Radiation Therapy Oncology Group (RTOG) protocols included in the secondary analysis by Blumenthal et al, with the effects of TTI beyond this interval not as well defined.¹⁶ The chi-squared test was performed to compare the proportion of patients within each covariate level across TTC groups.

Differences in OS stratified by RPA-defined TTC threshold (Fig. 2) and subsequent TTC categories (Supplementary Figure 1) were assessed using Kaplan-Meier methods and the log-rank test. Cox proportional hazards modeling was performed to identify covariates associated with OS. The proportional hazards assumption was tested for all covariates in the Cox proportional hazards model by considering correlation between survival time and Schoenfeld residuals.¹⁷ Covariates had an absolute correlation less than 0.10 and were assumed to follow the proportional hazards assumptions. We constructed a penalized spline function for TTC as the predictor of OS to characterize the impact

of TTC on OS as a continuous marker.¹⁸ Multivariable logistic regression was performed to identify covariates with prolonged TTC of adjuvant RT as defined by the RPA-determined optimal threshold. Statistical significance was defined by $\alpha < .05$. All statistical analyses were performed using the R statistical software, version 3.3.1.¹⁹

Results

Baseline Population Demographics

A total of 13489 patients meeting all inclusion and exclusion criteria were identified (Fig. 1). The median age of the study cohort was 60 years (interquartile range [IQR]: 53 to 68 years) with median follow-up time of 13.0 months (IQR: 6.5 to 21.8 months). Baseline patient demographic and treatment factors are presented in Table 1. The median TTC for the overall cohort was 43 days (IQR: 42 to 45 days), with

2025 patients (15.0%) completing adjuvant RT in more than 46 days from first treatment. Of patients with delayed TTC, 494 required more than 53 days to complete RT (3.7% overall). Groups stratified by TTC categorization varied significantly with respect to sex, race, insurance status, diagnosis year, and zip code income level.

Time to Completion and Survival

The median OS for the overall cohort was 13.7 months (95% confidence interval (CI) 13.4 to 14.0 months, Supplementary Figure 2). A threshold of 46.5 days for TTC of adjuvant RT associated with the greatest difference in OS for our cohort was identified using an RPA model fitting the full dataset with TTC as the sole predictor and confirmed as the median cutpoint from the RPA fits to 1000 training data sets. The median OS for patients with a TTC of 46 days or less was 14.0 months (95% CI 13.7 to 14.3 months) compared to a median OS of 12 months (95%

Fig. 2 Kaplan-Meier Survival Estimate for Patient Cohort Stratified by RPA-Defined Threshold for Time to Completion of Radiation Therapy. d indicates days; MOS, months; RPA, recursive partitioning analysis; TTC, time to completion.

CI 11.4 to 12.6 months) for patients with a TTC beyond this threshold ($P < .001$, [Figure 2](#)). The RPA-defined threshold of 46 days or less for completing adjuvant RT was used to delineate 3 categorizations for TTC: 40 to 46 days, 47 to 53 days, and 54 to 90 days from first to last fraction of RT. The median OS for patients with TTC between 47 to 53 days and between 54 and 90 days were 12.0 months (95% CI 11.3 to 12.8 months) and 11.8 months (95% CI 10.8 to 13.1 months), respectively ($P < .001$, [Supplementary Figure 3](#)).

In a multivariable Cox regression analysis, TTC of 47 to 53 days (HR 1.15, 95% CI 1.09 to 1.22, $P < .001$) and TTC of 54 to 90 days (HR 1.15, 95% CI 1.04 to 1.27, $P = .005$) were both associated with increased hazard of death compared to TTC between 40 to 46 days (reference group, [Table 2](#)) while controlling for other confounders that affect OS. A separate Cox model constructed to characterize the association between TTC as a continuous marker and OS demonstrated risk of death increased steeply from TTC of 40 days to beyond 50 days ([Fig. 3](#)).

Predictors of Prolonged Time to Completion

Multivariable logistic regression identified TTI, sex, race, insurance status, diagnosis year, and zip code income level as covariates associated with prolonged TTC (defined using the RPA-determined threshold of $TTC > 46$ days) in our population ([Table 3](#)). Patients with a TTI of 22 to 43 days were less likely to have prolonged TTC (odds ratio (OR) 0.66, 95% CI 0.59 to 0.74) compared to those with a TTI of 1 to 21 days (reference). Women were more likely to have a prolonged TTC (OR 1.20, 95% CI 1.09 to 1.32) than men (reference group). Uninsured patients (OR 1.41, 95% CI 1.10

to 1.80) and those with government insurance (OR 1.23, 95% CI 1.09 to 1.38) were more likely to have prolonged TTC with respect to patients with private insurance (reference). Black patients were more likely to have prolonged TTC (OR 1.45, 95% CI 1.19 to 1.77) compared to white patients in our cohort (reference group). Age, facility type, distance to treatment facility, and Charlson/Deyo comorbidity score were not associated with prolonged TTC in this study (all P values $> .05$).

Additional Covariates Associated with Survival

Multivariable Cox regression identified TTI, age, sex, race, Hispanic ethnicity, insurance status, facility type, Charlson/Deyo comorbidity, and zip code income level in addition to TTC as covariates significantly associated with OS in this study ([Table 2](#)). Initiation of adjuvant RT between 22 and 42 days from surgical resection was associated with decreased hazard of death (HR 0.92, 95% CI 0.88 to 0.96, $P = .002$) compared to patients initiating RT between 1 to 21 days from surgical resection (reference group). Diagnosis year and distance to treatment facility were not associated with OS in our population (P values $> .05$).

Discussion

In this analysis of the NCDB, we found delays prolonging the overall duration of adjuvant RT in patients with newly diagnosed GBM, receiving conventionally fractionated CRT, negatively affected survival. An RPA-determined threshold of 46 days for TTC of adjuvant RT was identified beyond which survival was significantly worsened with an

Table 1 Baseline Patient Demographics

	N	Prop (%)	N	Prop (%)	N	Prop (%)	N	Prop (%)	P_{χ^2}	Q1	Med	Q3	PKW
	Overall Cohort		TTI Groups										
Time to Treatment Completion			40–46 days		47–53 days		54+ days			42	43	45	
	13489		11464	85.0%	1531	11.3%	494	3.7%					
Time to Treatment Initiation									< .001				< .001
1-21 days	3044	22.6%	2471	81.2%	388	12.7%	185	6.1%		43	43	45	
22-42 days	8913	66.1%	7738	86.8%	924	10.4%	251	2.8%		42	43	44	
43+ days	1532	11.4%	1255	81.9%	219	14.3%	58	3.8%		43	43	45	
Age									.439				.156
(18-40)	731	5.4%	627	85.8%	76	10.4%	28	3.8%		42	43	45	
(40-50)	1671	12.4%	1422	85.1%	184	11.0%	65	3.9%		42	43	45	
(50-60)	3880	28.8%	3296	84.9%	440	11.3%	144	3.7%		42	43	45	
(60-70)	4471	33.1%	3830	85.7%	497	11.1%	144	3.2%		42	43	45	
(70+)	2736	20.3%	2289	83.7%	334	12.2%	113	4.1%		43	43	45	
Sex									.009				.012
Male	8131	60.3%	6984	85.9%	876	10.8%	271	3.3%		42	43	45	
Female	5358	39.7%	4480	83.6%	655	12.2%	223	4.2%		43	43	45	
Race									.001				.002
White	X	92.1%	10596	85.3%	1383	11.1%	X	3.6%		42	43	45	
Black	X	4.9%	523	78.6%	105	15.8%	X	5.6%		43	43	45	
Asian	X	1.5%	187	89.5%	16	7.7%	X	2.9%		43	43	44	
Other	X	1.4%	158	81.9%	27	14.0%	X	4.1%		42	43	45	
Hispanic Origin									.637				.068
Non-Hispanic	12928	95.8%	10995	85.0%	1462	11.3%	471	3.6%		42	43	45	
Hispanic	561	4.2%	469	83.6%	69	12.3%	23	4.1%		43	43	45	
Insurance Status									< .001				< .001
Private Insurance	7580	56.2%	6540	86.3%	775	10.2%	265	3.5%		42	43	44	
Not Insured	477	3.5%	386	80.9%	73	15.3%	18	3.8%		43	44	45	
Government	5432	40.3%	4538	83.5%	683	12.6%	211	3.9%		43	43	45	
Facility Type									.011				.004
Academic	X	43.4%	X	85.4%	X	10.6%	X	3.9%		42	43	44	
Community	X	44.1%	X	84.5%	X	12.0%	X	3.5%		43	43	45	
Integrated	X	6.9%	X	84.8%	X	12.6%	X	2.6%		43	43	45	
Other	X	0.1%	X	60.0%	X	26.7%	X	13.3%		43	44	49	
Suppressed (age < 40)	X	5.4%	X	85.8%	X	10.4%	X	3.8%		42	43	45	
Distance to Treatment Facility									.164				.002
(0-50)	11811	87.6%	10035	85.0%	1344	11.4%	432	3.7%		42	43	45	
(50-100)	1063	7.9%	899	84.6%	131	12.3%	33	3.1%		43	43	45	
(100+)	615	4.6%	530	86.2%	56	9.1%	29	4.7%		42	43	44	
Charlson/Deyo Comorbidity Score									.303				.015
0	10268	76.1%	8765	85.4%	1139	11.1%	364	3.5%		42	43	45	
1	2024	15.0%	1696	83.8%	247	12.2%	81	4.0%		43	43	45	
2+	1197	8.9%	1003	83.8%	145	12.1%	49	4.1%		43	43	45	

Table 1 Continued

	N	Prop (%)	N	Prop (%)	N	Prop (%)	N	Prop (%)	P_{χ^2}	Q1	Med	Q3	P KW
	Overall Cohort		TTI Groups										
Diagnosis Year									.003				< .001
2005	1030	7.6%	856	83.1%	139	13.5%	35	3.4%		43	44	45	
2006	1230	9.1%	1023	83.2%	157	12.8%	50	4.1%		43	43	45	
2007	1405	10.4%	1178	83.8%	178	12.7%	49	3.5%		43	43	45	
2008	1561	11.6%	1304	83.5%	188	12.0%	69	4.4%		42	43	45	
2009	1685	12.5%	1425	84.6%	200	11.9%	60	3.6%		42	43	45	
2010	2041	15.1%	1728	84.7%	226	11.1%	87	4.3%		42	43	45	
2011	2215	16.4%	1930	87.1%	209	9.4%	76	3.4%		42	43	44	
2012	2322	17.2%	2020	87.0%	234	10.1%	68	2.9%		42	43	44	
Zip Code Income Level									.003				.003
(\$63K-+)	4840	35.9%	4180	86.4%	496	10.2%	164	3.4%		42	43	44	
(\$48K-63K)	3908	29.0%	3349	85.7%	416	10.6%	143	3.7%		42	43	45	
(\$38K-\$48K)	2991	22.2%	2494	83.4%	380	12.7%	117	3.9%		42	43	45	
(0-\$38K)	1750	13.0%	1441	82.3%	239	13.7%	70	4.0%		42	43	45	

Abbreviations: KW, Kruskal-Wallis; Med, median; Q1, first quartile; Q3, third quartile; TTI, time to initiation.

Values denoted with "X" represent single-digit values redacted per the National Cancer Database data use agreement.

absolute difference in median OS of 2.0 months. Patients with TTC between 47 and 53 days had an increased hazard of death compared to patients with TTC between 40 and 46 days by multivariable Cox analysis. Delays were not uncommon in this cohort, with 2025 patients (15.0%) completing RT beyond 46 days from initiation.

The results of our analyses are consistent with previous investigations demonstrating adverse outcomes associated with prolonged courses of RT for NSCLC,⁵⁻⁷ uterine cervical carcinoma,⁸ and head and neck carcinoma.^{9,10} Two separate, pooled, secondary analyses of RTOG protocols using RT alone and CRT for patients with locally advanced NSCLC have demonstrated even short delays prolonging radiation treatment time by >4 to 5 days were associated with worsened OS for at least select patients.^{5,6} Perez et al examined 1224 patients with uterine cervical carcinoma and demonstrated prolonged radiation treatment time was associated with worsened locoregional control and cause-specific survival.⁸ Shaikh et al performed a recent analysis of the NCDB to determine the impact of radiation treatment time for patients with head and neck cancer. In a cohort of 19521 patients treated with definitive RT, CRT or surgical resection with postoperative RT, the authors demonstrated prolonged radiation treatment time was significantly associated with worsened survival in each treatment group.⁹

The effects of protracted adjuvant RT on survival for patients with GBM are less studied. Clinical trials investigating outcomes with split-course regimens of RT, intentionally incorporating breaks during RT, have not demonstrated improved outcomes,^{20,21} with an older series suggesting worsened survival with split-course compared to conventional fractionation for patients with GBM.²² Seidlitz and colleagues performed a retrospective analysis

of 369 patients with GBM treated with adjuvant RT or CRT at a single institution from 2001 to 2014 to characterize the clinical impact of delays prolonging RT.³ Radiation treatment time in their cohort ranged from 40 to 71 days with a median of 45 days. In contrast to our results, radiation treatment time was not significantly associated with survival in their cohort by Cox regression analysis ($P = .225$). Although this well-conducted study included a relatively large cohort of patients with GBM, only 39 patients (8.9%) had a radiation treatment time beyond 50 days. As such, this may have been an insufficient sample size to detect a detriment to clinical outcomes with prolonged RT time. The authors acknowledged this limitation by stating their study could not in fact characterize the effect of delays prolonging RT time beyond 50 days.

Identifying factors that may be associated with delays during adjuvant RT is important to contextualize the survival impact of prolonged TTC of RT for patients with GBM, particularly in a retrospective study. Previous investigations have shown sources contributing to unplanned interruptions prolonging RT can be grouped into 2 general strata: health-related factors including intercurrent illness and treatment toxicity, and nonhealth-related factors such as holidays, machine breakdown, and difficulties with transportation.¹⁻⁴ Increased burden of intercurrent disease and treatment toxicity may of course hinder survival independent of any delays to treatment they may cause.

Poor outcomes associated with nonhealth-related delays could potentially be explained by tumor radiobiologic principles. The hazard of accelerated repopulation, characterizing the response of malignant cells including increased mitotic rate to cytotoxic injury, has been well described for cancer subtypes including squamous cell carcinoma

Table 2 Multivariable Cox Proportional Hazards Analysis for Overall Survival

Covariates	HR	LHR	UHR	Factor P Value	Term P Value
Time to Treatment Initiation				.002	
1-21 days	Reference				
22-42 days	0.92	0.88	0.96		.002
43+ days	0.97	0.91	1.04		.415
Time to Treatment Completion				< .001	
40-46 days	Reference				
47-53 days	1.15	1.09	1.22		< .001
54-90 days	1.15	1.04	1.27		.005
Age				< .001	
(18-40)	Reference				
(40-50)	1.51	1.35	1.68		< .001
(50-60)	1.86	1.68	2.05		< .001
(60-70)	2.26	2.05	2.50		< .001
(70-+)	3.03	2.72	3.38		< .001
Sex				< .001	
Male	Reference				
Female	0.85	0.82	0.89		< .001
Race				.002	
White	Reference				
Black	0.89	0.82	0.98		.015
Asian	0.74	0.63	0.88		.004
Other	0.96	0.82	1.13		.660
Hispanic Origin				< .001	
Non-Hispanic	Reference				
Hispanic	0.78	0.71	0.86		< .001
Insurance Status				< .001	
Private Insurance	Reference				
Not Insured	1.02	0.92	1.14		.672
Government	1.13	1.08	1.19		< .001
Facility Type				< .001	
Academic	Reference				
Community	1.11	1.07	1.16		< .001
Integrated	1.12	1.04	1.21		.003
Other	1.11	0.66	1.88		.695
Suppressed (age < 40)					
Distance to Treatment Facility				.539	
(0-50)	Reference				
(50-100)	1.02	0.95	1.09		.619
(100-+)	0.96	0.87	1.05		.350
Charlson/Deyo Comorbidity Score				< .001	
0	Reference				
1	1.15	1.09	1.21		< .001
2+	1.27	1.19	1.35		< .001
Diagnosis Year				.195	
2005	Reference				
2006	0.98	0.90	1.07		.628
2007	1.00	0.92	1.09		.975

Table 2 Continued

Covariates	HR	LHR	UHR	Factor <i>P</i> Value	Term <i>P</i> Value
2008	0.97	0.89	1.05		.429
2009	0.94	0.87	1.03		.172
2010	0.93	0.85	1.00		.059
2011	0.93	0.86	1.01		.069
2012	0.92	0.85	1.00		.056
Zip Code Income Level				< .001	
(\$63K-+)	Reference				
(\$48K-63K)	1.08	1.03	1.13		.007
(\$38K-\$48K)	1.17	1.11	1.23		< .001
(0-\$38K)	1.15	1.08	1.23		< .001

Abbreviations: HR, hazard ratio; LHR, lower limit of 95% confidence interval for hazard ratio; UHR, upper limit of 95% confidence interval for hazard ratio.

Fig. 3 Spline Cox Proportional Hazards Regression Model Depicting Adjusted Hazard Ratios of Overall Mortality With Respect to Increasing Time to Completion as a Continuous Variable, With Interrupted Lines Representing 95% Confidence Intervals

of the head and neck during treatment with conventionally fractionated RT.²³ Analysis of GBM cell lines demonstrated the ability of these cells to repopulate during a fractionated course of RT under in vitro conditions.²⁴ Pedicini et al performed mathematical modeling to better define radiobiologic parameters including capacity for accelerated repopulation in GBM using clinical trial outcomes.²⁵ Their results suggest a kickoff time of 37 days, defined as the interval from initiation of adjuvant RT until the initiation of accelerated repopulation, for patients with GBM. Given the association between TTC of adjuvant RT beyond 46 days from initiation and worsened OS in our study, accelerated

repopulation would be in the correct time frame to serve as a potential mechanism underlying the detriment to OS with prolonged TTC.

Furthermore, RT has been demonstrated in vitro and in animal GBM models to induce genetic changes that may contribute to a more adaptive phenotype with greater potential for invasive growth in surviving cells.^{26,27} Aberrant activation of the MET tyrosine kinase receptor signaling pathway has been associated with tumor growth, invasion, and angiogenesis in solid tumors including GBM.^{28,29} De Bacco and colleagues used both human glioma cell lines and mice xenograft models to show RT induced abnormal

Table 3 Multivariable Logistic Regression Model for Predictors of Prolonged TTC

Covariates	OR	LOR	UOR	Factor <i>P</i> Value	Term <i>P</i> Value
Time to Treatment Initiation				< .001	
1-21 days	Reference				
22-42 days	0.66	0.59	0.74		< .001
43+ days	0.94	0.80	1.10		.432
Age				.423	
(18-40)	Reference				
(40-50)	1.07	0.83	1.38		.602
(50-60)	1.08	0.86	1.37		.498
(60-70)	0.98	0.77	1.24		.856
(70+)	1.04	0.80	1.34		.774
Sex				.003	
Male	Reference				
Female	1.20	1.09	1.32		.003
Race				.009	
White	Reference				
Black	1.45	1.19	1.77		.002
Asian	0.73	0.46	1.14		.160
Other	1.26	0.87	1.83		.224
Hispanic Origin				.689	
Non-Hispanic	Reference				
Hispanic	1.05	0.83	1.33		.689
Insurance Status				.003	
Private Insurance	Reference				
Not Insured	1.41	1.10	1.80		.006
Government	1.23	1.09	1.38		.001
Facility Type				.151	
Academic	Reference				
Community	1.02	0.92	1.13		.747
Integrated	1.02	0.84	1.23		.880
Other	3.71	1.30	10.56		.014
Suppressed (age < 40)					
Distance to Treatment Facility				.606	
(0-50)	Reference				
(50-100)	0.98	0.82	1.17		.804
(100+)	0.89	0.70	1.13		.329
Charlson/Deyo Comorbidity Score				.264	
0	Reference				
1	1.11	0.97	1.27		.119
2+	1.06	0.90	1.26		.457
Diagnosis Year				.006	
2005	Reference				
2006	1.01	0.81	1.26		.934
2007	0.96	0.77	1.19		.711
2008	0.99	0.80	1.23		.953
2009	0.93	0.75	1.15		.497
2010	0.94	0.77	1.16		.574
2011	0.77	0.63	0.95		.013
2012	0.77	0.63	0.95		.013

Table 3 Continued

Covariates	OR	LOR	UOR	Factor <i>P</i> Value	Term <i>P</i> Value
Zip Code Income Level				.015	
(\$63K+)	Reference				
(\$48K-63K)	1.02	0.90	1.15		.792
(\$38K-\$48K)	1.19	1.04	1.35		.011
(0-\$38K)	1.21	1.03	1.41		.018

Abbreviations: LHR, lower limit of 95% confidence interval for odds ratio; OR, odds ratio; TTC, time to completion; UHR, upper limit of 95% confidence interval for odds ratio.

activation of this signaling pathway.²⁶ Additionally, RT may select for more radioresistant GBM clonal populations, with tumors displaying different molecular profiles at relapse compared to mutational profiles at time of diagnosis.³⁰ Unplanned interruptions during RT may conceivably allow for repopulation of treatment-resistant clonogens with mutational changes associated with invasive growth and angiogenesis. The clinical implications of these findings, however, are areas of active investigation and have not been fully characterized. The hazard of delays during RT and the potential for accelerated repopulation with selected, treatment-resistant GBM clonogens merits further investigation with clinical and translational studies.

Unfortunately, there was not sufficient granularity in the dataset to characterize health-related and nonhealth-related factors that likely contributed to prolonged TTC of adjuvant RT in our population. Subsequently, we were unable to control for these factors in our analyses. Despite this limitation, we extracted available patient demographic and treatment-related factors from the database and controlled for these variables in a multivariate logistic regression to identify predictors of prolonged TTC. Insurance status and zip code income level were both identified and may be correlated with a patient population particularly at risk for experiencing unplanned delays leading to prolonged TTC of RT, with the relationship between adverse socioeconomic factors and unplanned interruptions in RT having been previously characterized.⁴ Though beyond the scope of this study, further characterization of health-related and nonhealth-related factors associated with delays in completing RT for patients with GBM is of acknowledged interest and requires additional investigation.

We performed a robust analysis using a large, national database and demonstrated delays prolonging completion of conventionally fractionated adjuvant RT were associated with worsened survival for patients with GBM. While these results are compelling, there are limitations in addition to the inability to further define sources of delay prolonging TTC in our analyses that warrant further discussion. Validated prognostic factors associated with OS including baseline patient performance status were unavailable in the dataset, and it is possible these prognostic factors were not equivalently distributed in subgroups stratified by TTC. Though Charlson/Deyo comorbidity scores did not significantly vary between TTC subgroups in our population and this covariate was controlled for in our analyses, there may be differences in baseline intercurrent disease burden

between subgroups stratified by TTC not captured by this measure. Additionally, it is unclear if prolonged TTC is driving worsened outcomes for these patients or serves as a marker associated with prognostic factors such as poorer baseline performance status and increased intercurrent disease burden independently associated with decreased OS. Given relatively few patients in our cohort completed RT ≥ 54 days, our results did not demonstrate a further increased hazard of death with delays prolonging the completion of adjuvant RT beyond this interval.

Further limitations include the unavailability of additional validated clinical and molecular prognostic factors such as extent of surgical resection, O⁶-methylguanine-DNA-methyltransferase (*MGMT*) promoter methylation status, and isocitrate dehydrogenase-1 (*IDH-1*) mutation status in the dataset. We were also unable to restrict our cohort to patients receiving adjuvant CRT with concomitant and adjuvant temozolomide given insufficient granularity in the dataset regarding specific CT agent administered and schedule of CT administration. Additionally, the NCDB collects only information regarding the initial course of therapy, restricting analysis of TTC and disease progression and other cancer-specific clinical outcomes. We were unable to control for additional courses of treatment at time of disease progression including re-resection and re-irradiation in this analysis, potentially modulating survival in our cohort.

Despite these acknowledged limitations, analysis of a large, national database containing hospital-level data may be optimal to examine the impact of prolonged TTC of adjuvant RT on OS for patients with GBM in lieu of level I evidence from randomized clinical data. A prospective trial investigating the impact of prolonged TTC on clinical outcomes for patients with GBM remains unlikely because of lack of clinical equipoise. Further, the size and diversity of the study cohort captured in the NCDB may be better representative of treatment and clinical outcomes for the overall population of adults with GBM in the United States than investigations of patients meeting eligibility criteria for enrollment on clinical trials or treated at a single institution.

Conclusions

In summary, we performed an analysis of the NCDB and demonstrated delays prolonging completion of adjuvant

RT were detrimental to survival for adults with newly diagnosed GBM treated with conventionally fractionated adjuvant CRT. An RPA-defined threshold of 46 days from surgical resection to completion of adjuvant RT was identified, beyond which survival was worsened with an absolute difference in median OS of 2 months.

ProlongedTTC was relatively common in our cohort with 15.0% of patients completing adjuvant RT beyond 46 days from initiation. Our results suggest any unnecessary delays during adjuvant RT for these patients should be minimized while ensuring safe delivery of therapy. Validation of these findings with pooled, secondary analyses of clinical trials or large, single-institution experiences are needed to more fully characterize the impact of prolonged TTC of adjuvant RT on OS for patients with GBM. Future studies are also needed to examine the impact of prolonged TTC on progression-free survival and further define health-related and nonhealth-related factors associated with unplanned interruptions during adjuvant RT for these patients.

Supplementary Material

Supplementary material is available at *Neuro-Oncology* online.

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References

1. Stupp R, Mason WP, van den Bent MJ, et al; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987–996.
2. Sijben AE, McIntyre JB, Roldán GB, et al. Toxicity from chemoradiotherapy in older patients with glioblastoma multiforme. *J Neurooncol*. 2008;89(1):97–103.
3. Seidlitz A, Siepmann T, Löck S, Juratli T, Baumann M, Krause M. Impact of waiting time after surgery and overall time of postoperative radiochemotherapy on treatment outcome in glioblastoma multiforme. *Radiat Oncol*. 2015;10:172.
4. Ohri N, Rapkin BD, Guha D, et al. Predictors of radiation therapy non-compliance in an urban academic cancer center. *Int J Radiat Oncol Biol Phys*. 2015;91(1):232–238.
5. Cox JD, Pajak TF, Asbell S, et al. Interruptions of high-dose radiation therapy decrease long-term survival of favorable patients with unresectable non-small cell carcinoma of the lung: analysis of 1244 cases from 3 Radiation Therapy Oncology Group (RTOG) trials. *Int J Radiat Oncol Biol Phys*. 1993;27(3):493–498.
6. Machtay M, Hsu C, Komaki R, et al. Effect of overall treatment time on outcomes after concurrent chemoradiation for locally advanced non-small-cell lung carcinoma: analysis of the Radiation Therapy Oncology Group (RTOG) experience. *Int J Radiat Oncol Biol Phys*. 2005;63(3):667–671.
7. McMillan MT, Ojerholm E, Verma V, et al. Radiation treatment time and overall survival in locally advanced non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2017;98(5):1142–1152.
8. Perez CA, Grigsby PW, Castro-Vita H, Lockett MA. Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. *Int J Radiat Oncol Biol Phys*. 1995;32(5):1275–1288.
9. Shaikh T, Handorf EA, Murphy CT, Mehra R, Ridge JA, Galloway TJ. The impact of radiation treatment time on survival in patients with head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2016;96(5):967–975.
10. Rosenthal DI, Liu L, Lee JH, et al. Importance of the treatment package time in surgery and postoperative radiation therapy for squamous carcinoma of the head and neck. *Head Neck*. 2002;24(2):115–126.
11. Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. *Ann Surg Oncol*. 2008;15(3):683–690.
12. LeBlanc M, Crowley J. Relative risk trees for censored survival data. *Biometrics*. 1992;48(2):411–425.
13. Han SJ, Rutledge WC, Molinaro AM, et al. The effect of timing of concurrent chemoradiation in patients with newly diagnosed glioblastoma. *Neurosurgery*. 2015;77(2):248–253; discussion 253.
14. Wang TJ, Jani A, Estrada JP, et al. Timing of adjuvant radiotherapy in glioblastoma patients: a single-institution experience with more than 400 patients. *Neurosurgery*. 2016;78(5):676–682.
15. Spratt DE, Folkert M, Zumsteg ZS, et al. Temporal relationship of postoperative radiotherapy with temozolomide and oncologic outcome for glioblastoma. *J Neurooncol*. 2014;116(2):357–363.
16. Blumenthal DT, Won M, Mehta MP, et al. Short delay in initiation of radiotherapy may not affect outcome of patients with glioblastoma: a secondary analysis from the radiation therapy oncology group database. *J Clin Oncol*. 2009;27(5):733–739.
17. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994;81(3):515–526.
18. Paul HCE, Marx BD. Flexible smoothing with *B*-splines and penalties. *Stat Sci*. 1996;11(2):89–102.
19. *R: A Language and Environment for Statistical Computing [computer program]*. Version 3.1.2. Vienna, Austria: R Foundation for Statistical Computing; 2016.
20. Rao RD, Thomé SD, O'Fallon J, Earle JD, Dinapoli RP, Buckner JC. Safety of thrice-daily hyperfractionated radiation and BCNU for high-grade gliomas. *Int J Radiat Oncol Biol Phys*. 2002;53(2):376–384.
21. Groves MD, Maor MH, Meyers C, et al. A phase II trial of high-dose bromodeoxyuridine with accelerated fractionation radiotherapy followed by procarbazine, lomustine, and vincristine for glioblastoma multiforme. *Int J Radiat Oncol Biol Phys*. 1999;45(1):127–135.
22. Aristizabal SA, Caldwell WL. Time-dose-volume relationships in the treatment of glioblastoma multiforme. *Radiology*. 1971;101(1):201–202.
23. Withers HR, Taylor JM, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. *Acta Oncol*. 1988;27(2):131–146.
24. Budach W, Gioioso D, Taghian A, Stuschke M, Suit HD. Repopulation capacity during fractionated irradiation of squamous cell carcinomas and glioblastomas in vitro. *Int J Radiat Oncol Biol Phys*. 1997;39(3):743–750.
25. Pedicini P, Fiorentino A, Simeon V, et al. Clinical radiobiology of glioblastoma multiforme: estimation of tumor control probability from various radiotherapy fractionation schemes. *Strahlenther Onkol*. 2014;190(10):925–932.

26. De Bacco F, Luraghi P, Medico E, et al. Induction of MET by ionizing radiation and its role in radioresistance and invasive growth of cancer. *J Natl Cancer Inst.* 2011;103(8):645–661.
27. Dahan P, Martinez Gala J, Delmas C, et al. Ionizing radiations sustain glioblastoma cell dedifferentiation to a stem-like phenotype through survivin: possible involvement in radioresistance. *Cell Death Dis.* 2014;5:e1543.
28. Boccaccio C, Comoglio PM. Invasive growth: a MET-driven genetic programme for cancer and stem cells. *Nat Rev Cancer.* 2006;6(8):637–645.
29. Abounader R, Laterra J. Scatter factor/hepatocyte growth factor in brain tumor growth and angiogenesis. *Neuro Oncol.* 2005;7(4):436–451.
30. Wang J, Cazzato E, Ladewig E, et al. Clonal evolution of glioblastoma under therapy. *Nat Genet.* 2016;48(7):768–776.