Neuro-Oncology
20(7), 966–974, 2018 | doi:10.1093/neuonc/noy017 | Advance Access date 15 February 2018

Short delay in initiation of radiotherapy for patients with glioblastoma-effect of concurrent chemotherapy: a secondary analysis from the NRG Oncology/Radiation Therapy Oncology Group database

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Abstract

Background: We previously reported the unexpected finding of significantly improved survival for newly diagnosed glioblastoma in patients when radiation therapy (RT) was initiated later (>4 wk post-op) compared with earlier (≤2 wk post-op). In that analysis, data were analyzed from 2855 patients from 16 NRG Oncology/Radiotherapy Oncology Group (RTOG) trials conducted prior to the era of concurrent temozolomide (TMZ) with RT. We now report on 1395 newly diagnosed glioblastomas from 2 studies, treated with RT and concurrent TMZ followed by adjuvant TMZ. Our hypothesis was that concurrent TMZ has a synergistic/radiosensitizing mechanism, making RT timing less significant.

Methods: Data from patients treated with TMZ-based chemoradiation from NRG Oncology/RTOG 0525 and 0825 were analyzed. An analysis comparable to our prior study was performed to determine whether there was still an impact on survival by delaying RT. Overall survival (OS) was investigated using the Kaplan–Meier method and Cox proportional hazards model. Early progression (during time of diagnosis to 30 days after RT completion) was analyzed using the chi-square test.

Results: Given the small number of patients who started RT early following surgery, comparisons were made between >4 and ≤4 weeks delay of radiation from time of operation. There was no statistically significant difference in OS (hazard ratio = 0.93; $P = 0.29$; 95% CI: 0.80–1.07) after adjusting for known prognostic factors (recursive partitioning analysis and O^6-methylguanine-DNA methyltransferase methylation status). Similarly, the rate of early progression did not differ significantly ($P = 0.63$).

Conclusions: We did *not* observe a significant prognostic influence of delaying radiation when given concurrently with TMZ for newly diagnosed glioblastoma. The effects of early (1–3 wk post-op) or late (>5 wk) initiation of radiation tested in our prior study could not be replicated.

Keywords

chemoradiation | delay | glioblastoma | survival | temozolomide

Importance of the study

Glioblastomas are rapidly growing neoplasms, and many patients and families assume that adjuvant therapy must begin immediately following surgery, with every day of delay detrimental to survival; this presumption is reinforced in some cases by the treating physician. Therefore, having relevant data available can be of great logistical help in treatment planning. Our present study of the impact of delay of initiation of treatment in the era of concurrent chemoradiation adds to our original findings for similar patients treated with radiation monotherapy, for whom delay (up to 6 wk from surgery) of initiating treatment was surprisingly beneficial. In this study, we found that a short delay in beginning chemoradiation was neither beneficial nor detrimental.

Until the mid-2000s, irradiation alone was the established standard for treatment of newly diagnosed glioblastoma (GBM). Clinical trials of patients receiving radiation therapy (RT) for GBM have led to a doubling of overall survival (OS) compared with patients who did not receive RT.[1] Results of a phase III trial published by the European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada (EORTC/NCIC) in 2005[2] led to the uniformly adopted treatment standard for newly diagnosed GBM: addition of temozolomide (TMZ) to the front-line regimen concurrent with external beam conformal radiation, followed by 6 adjuvant 5-day monthly cycles of TMZ. While there remains a subset of patients whose tumors do not benefit from treatment with RT and who progress during the first-line RT/TMZ period, the benefit of radiation for the standard adult population in newly diagnosed GBM is not disputed.

Further prospective phase III trials (NRG Oncology/RTOG 0525 and 0825) have validated the impact of adding TMZ to first-line therapy for GBM, with progression-free survival (PFS) and OS data similar to those seen on the RT/TMZ arm of the initially published study (ie, superior to treatment with radiation alone).

Prior work by our group[3] showed that a short delay in the initiation of radiation for treatment of newly diagnosed GBM was not detrimental. In fact, we observed an unexpected progressive-linear benefit in median OS for delaying radiation treatment from 0–2 weeks to 6 weeks postoperatively. While the phenomenon described was thought-provoking, our prior work was based on data from NRG Oncology/RTOG trials for newly diagnosed GBM with RT alone arms, before TMZ became commonly used as standard first-line therapy in the clinic and in research trials. Thus, it is unclear whether our previous conclusions are germane in an era where almost all patients diagnosed with GBM receive not only RT but also concurrent chemotherapy.

Our objective with this study was to examine the impact of short delay (up to 6 wk) of RT initiation on survival outcome, in patients with newly diagnosed GBM treated on the RT/TMZ arms in the context of 2 large NRG Oncology/RTOG phase III trials. Our working hypothesis was that addition of TMZ to radiation would lessen the impact of the timing of initiating first-line therapy after surgery.

Methods

Data were analyzed from patients with newly diagnosed GBM treated using standard chemoradiation (TMZ 75 mg/kg daily with 60 Gy external beam radiation). We utilized data obtained from both arms of RTOG 0525 and the placebo arm of RTOG 0825. In addition, the analyses included patients who were eligible for the respective studies, started the standard concurrent chemoradiation, but did not reach the randomization stage due to reasons such as early progression/death, consent withdrawal, etc. RTOG 0525 was a phase III trial which compared conventional adjuvant TMZ with dose-intensive TMZ in patients with newly diagnosed GBM.[4] Patients were randomized after successful completion of concurrent chemoradiation, which was required to begin less than 5 weeks postoperatively. The clinical dataset used is from January 6, 2011. By that time, 80% of all the eligible patients had died, and 91% had either progressed or died without disease progression. RTOG 0825 was a phase III double-blind, placebo-controlled trial of conventional concurrent chemoradiation and adjuvant TMZ plus bevacizumab versus conventional concurrent chemoradiation and adjuvant TMZ in patients with newly diagnosed GBM.[5] Patients were randomized by 10 days after start of radiation. Radiation was required to begin after 3 weeks and less than 5 weeks from the date of surgery. The clinical dataset is from December 17, 2012. By

that time, 67% of all the eligible patients had died, and 81% had either progressed or died without disease progression.

We computed the time interval between surgery and initiation of RT. Patients were initially categorized into one of 3 groups: time interval ≤3 weeks, >3 and ≤4 weeks, or >4 weeks. Overall survival was defined as the interval from start of RT to death due to any cause or to the time when the patient was last reported alive. Frequency distributions of the patient pretreatment characteristics for the 3 groups of patients were compared using chi-square tests for categorical variables and Kruskal–Wallis tests for continuous variables. The Kaplan–Meier method was used to calculate the survival rates for each group of patients. Hazard ratios (HRs) on the timing of RT initiation were calculated using the stratified Cox proportional hazards model, with study (RTOG 0525 vs 0825) included as strata, and tested using log-rank tests.

Because the treatment start time was not a randomized event, specific host and tumor variables could have nonrandomly led to certain patients starting therapy earlier versus others starting later; to account for this disparity, multivariate analyses were conducted using the stratified Cox proportional hazards model, with patient pretreatment characteristics included as covariates (Supplementary Table S1). The time interval between surgery and the initiation of RT was also examined as a continuous variable. Early progression was defined as progression that occurred between start of RT and 30 days after RT completion, and rates of early progression versus progression after 30 days of RT completion were analyzed using the chi-square test.

Results

A retrospective analysis of 1463 patients (1125 from RTOG 0525 and 338 from RTOG 0825) comparable to our prior published study was performed to determine whether, with the addition of TMZ, there was still an impact on survival by delaying RT (+TMZ). Sixty-eight patients were excluded from the analysis due to no radiation (44) or chemotherapy received (21), or unknown surgery date (3), leaving 1395 patients with data available for analysis. Consort diagrams are shown for RTOG 0525 and 0825, respectively, in Supplementary Figures S1 and S2. The distribution of the time between surgery and the initiation of RT with the same grouping method applied as in the previous manuscript is listed in Table 1, segregated into 3 groups:

Table 1 Distribution of interval from surgery to RT start

Interval	RTOG 0525		RTOG 0825		Total	
	n	%	*N*	%	*n*	%
≤3 wk	173	16.0	13	4.1	186	13.3
>3–4 wk	345	32.0	119	37.7	464	33.3
>4 wk	561	52.0	184	58.2	745	53.4
Total	1079	100.0	316	100.0	1395	100.0

chemo-RT initiated ≤3 weeks; >3–4 weeks; and >4 weeks. Overall, only 2.2% and 2.5% of the patients initiated RT ≤2 and >5 weeks after surgery, respectively. Seven patients began chemo-RT >6 weeks from the time of surgery.

Shown in Table 2 are pretreatment characteristics (age, sex, Karnofsky performance status, prior surgery, neurologic function, recursive partitioning analysis [RPA], and O^6-methylguanine-DNA methyltransferase [MGMT] status) and RT dose by time interval from surgery to initiation of RT. The median ages ranged from 57 to 59 among the 3 different time interval groups, and median RT dose was 60 Gy for each of the groups. RPA stage and MGMT status are balanced among the 3 groups of patients. As expected, almost all the patients who started RT ≤3 weeks after surgery came from RTOG 0525.

Kaplan–Meier curves for OS between the 2 studies, RTOG 0525 and 0825, show similar survival results (Supplementary Figure S1), justifying combining patients from these 2 studies for the analysis.

The median time from surgery to RT start was approximately 4 weeks. Given the relatively small number of patients who started RT early following surgery, we used 4 weeks as a cutoff to further define 2 groups. Comparisons were ultimately made between >4 and ≤4 weeks delay of radiation from time of surgery. Median survival times were 16.0 months (95% CI: 15.1–17.1) for the >4-week group and 15.9 months (95% CI: 15.0–16.7) for the ≤4-week group, with HR = 0.96 (P = 0.52; 95% CI: 0.85–1.08). Fig. 1 shows the Kaplan–Meier curves on OS for the 2 groups. There was no statistically significant difference in OS between the 2 groups (HR = 0.95; P = 0.49; 95% CI: 0.84–1.09) after adjusting for known prognostic factors (RPA and MGMT methylation status) and other pretreatment characteristics (Table 3). Among the 1395 patients, 1019 (73.0%) have experienced disease progression, and 18.1% of those events were categorized as early progression. Similar to OS, the rate of early progression did not differ significantly (P = 0.63) between the 2 groups. Comparable results were found regarding the effect (or lack of effect) of delaying RT, following subgroup analyses performed by RPA class and by MGMT methylation status.

Overall survival comparisons were examined among 3 (smaller) different time interval groups (Fig. 2). Pairwise comparisons of OS between time intervals showed that there was no difference in each comparison in either univariate or multivariate analyses. No significant difference was found in the rate of early progression for the 3 group comparisons.

Time from surgery to start of RT was not shown to have a significant effect on OS, when analyzed as a continuous variable.[6] These data are shown in Supplementary Table S2.

Discussion

We previously reported the unexpected finding of significantly improved survival in patients with newly diagnosed GBM when radiation was initiated later (>4 wk post-op) compared with earlier (≤2 wk post-op).[3] In a prior controlled experiment in rat models undergoing cranial irradiation, increased tissue damage was observed when radiation therapy was delivered closer to the time of a

Table 2 Pretreatment characteristics

Patient or Tumor Characteristic	≤3 wk		>3–4 wk		>4 wk		*P*-value
	n	%	*n*	%	*n*	%	
Days from surgery to start of RT							
Median	19		26		33		
Min–Max	0–21		22–28		29–68		
Q1–Q3	16–21		24–27		31–35		
RT dose							0.42**
Median	60		60		60		
Min–Max	22–60.14		4–64		2–62		
Q1–Q3	60–60		60–60		60–60		
Age, y							0.24**
Median	59		58		57		
Min–Max	22–87		19–84		20–84		
Q1–Q3	51–66		50–65		50–65		
Sex							0.21*
Male	105	56.5	286	61.6	423	56.8	
Female	81	43.5	178	38.4	322	43.2	
Karnofsky performance status							0.32*
60	11	5.9	17	3.7	33	4.4	
70	23	12.4	57	12.3	89	11.9	
80	37	19.9	115	24.8	152	20.4	
90	87	46.8	183	39.4	311	41.7	
100	28	15.1	92	19.8	160	21.5	
Surgery	Partial vs total resection						0.003*
Partial resection	82	44.1	171	36.9	346	46.4	
Total resection	89	47.8	277	59.7	373	50.1	
Other	15	8.1	16	3.4	26	3.5	
Neurologic function	No vs minor vs moderate/severe symptoms						0.04*
No symptoms	46	24.7	141	30.4	260	34.9	
Minor symptoms	101	54.3	218	47.0	320	43.0	
Moderate symptoms	39	21.0	103	22.2	161	21.6	
Severe symptoms	0	0.0	2	0.4	4	0.5	
RPA	RPA III vs IV vs V						0.53*
III	28	15.1	77	16.6	138	18.5	
IV	111	59.7	288	62.1	450	60.4	
V	47	25.3	96	20.7	152	20.4	
Unknown	0	0.0	3	0.6	5	0.7	
MGMT status	Methylated vs unmethylated						0.70*
Methylated	46	24.7	120	25.9	209	28.1	
Unmethylated	105	56.5	267	57.5	422	56.6	
Unknown (indeterminate, invalid)	16	8.6	31	6.7	49	6.6	
Insufficient tissue	18	9.7	40	8.6	57	7.7	
Not done	1	0.5	6	1.3	8	1.1	
Radiotherapy delivery declared at registration							<0.001*
RTOG RT#	178	95.7	438	94.4	618	83.0	
EORTC RT##	8	4.3	26	5.6	127	17.0	

Table 2 *Continued*

Patient or Tumor Characteristic	≤3 wk		>3–4 wk		>4 wk		*P*-value
	n	%	*n*	%	*n*	%	
Study number							<0.001*
RTOG 0525	173	93.0	345	74.4	561	75.3	
RTOG 0825	13	7.0	119	25.6	184	24.7	
Total	186	100.0	464	100.0	745	100.0	

*Chi-square test.
**Kruskal–Wallis test.
RTOG RT: RTOG radiation guidelines assume a 2-phase plan (46 + 14 = 60 Gy), with a wider field in most cases, that includes the "edema"/infiltrative non-enhancing tumor: T2 area of hyperintensivity + T1 enhancing residual tumor + resection cavity + a 2 cm margin.
EORTC RT: EORTC radiation guidelines assume a 1-phase planned clinical target volume to treat T1 enhancing residual tumor + resection cavity + a 2–3 cm margin.

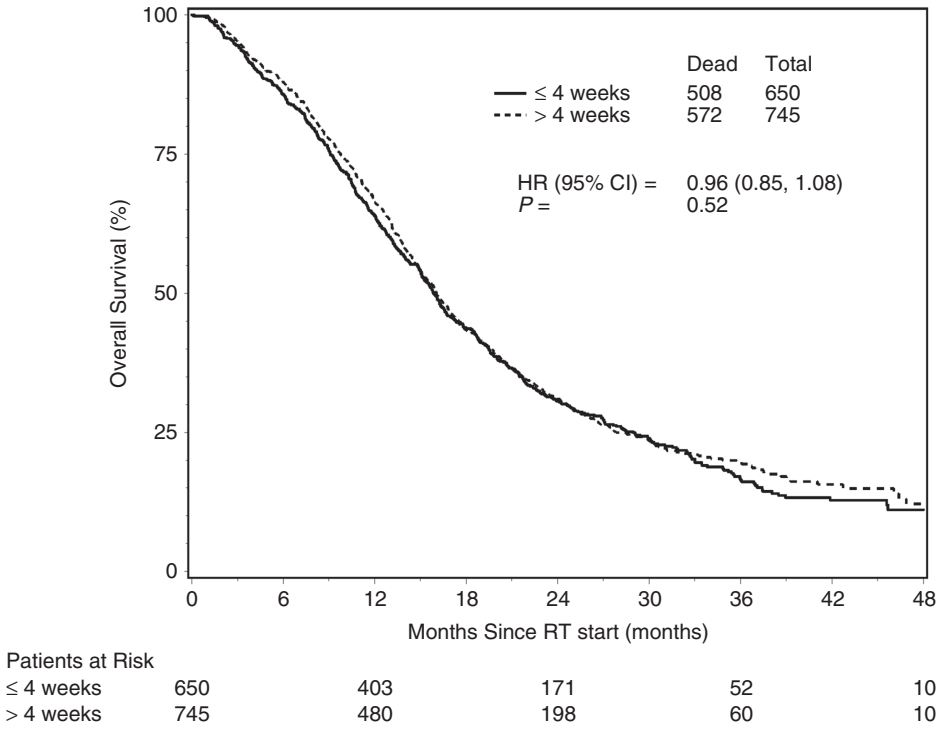

Fig. 1 Overall survival by 2 interval groups.

surgical procedure compared with a delay in radiation or with controls who did not receive radiation; it is speculatively possible that this observation may have implications relevant to our findings in the present analysis.[7] Our working hypothesis for this specific analysis was that concurrent TMZ has an additive or synergistic/radiosensitizing mechanism, rendering RT timing less significant than was seen in the results of our initial work done in the radiation monotherapy era.[3]

Temozolomide has been shown to provide significant additive effects in combination with radiation when exposing glioblastoma cell lines to the treatments, specifically at subtherapeutic levels of TMZ.[8]

The combination of the 2 modalities has been shown to have radiosensitizing effect (beyond additive) in selected cell lines when clinically therapeutic doses of TMZ are used.[9,10] Radiosensitization as measured by damage to the tumor cell DNA is significantly increased by combining TMZ and radiation compared with either modality alone. Inhibition of tumor growth is seen with an almost 3-fold increase of radiation dose enhancement in xenografts, with end results of tumor growth inhibition more than what would be expected by additive effects.[11] Temozolomide enhances radiosensitivity in vitro and in vivo, not via apoptosis but most likely via interference of mechanisms of DNA double-strand break repair.

We speculate that the impact of timing of initiating (chemo)radiation is less important in light of radiosensitizing effect of TMZ compared with radiation treatment as monotherapy for newly diagnosed glioblastoma.

Other recently published, smaller retrospective reports have examined the effect of postsurgical therapy initiation for GBM in the TMZ era and concur with our findings of no significant benefit or detriment for delaying initiation of chemoradiation therapy within the guidelines of 6 weeks (a criterion typically required for participation in a prospective clinical trial for first-line therapy of GBM)[12–17] (see Table 4).

Only one study of 345 GBM patients treated at Memorial Sloan-Kettering Cancer Center showed discrepant findings:

Table 3 Cox proportional hazards model for OS (multivariate) using 2 interval groups

Variable (**bolded** value has **unfavorable** outcome)	*P*-value	Hazard Ratio (95% CI)
Time from surgery to start of RT (>4 wk vs ≤**4 wk**)	0.490	0.95 (0.84, 1.09)
RPA (**IV** vs III)	<0.001	1.65 (1.37, 1.99)
RPA (**V** vs III)	<0.001	2.91 (2.34, 3.61)
MGMT status **(unmethylated** vs methylated)	<0.001	1.72 (1.48, 2.00)
Sex (**male** vs female)	<0.001	1.31 (1.14, 1.50)

Model derived from stepwise selection.

a multivariate analysis including MGMT status showed that delaying the onset of chemoradiation was associated with decreased OS, particularly when therapy was delayed beyond 6 weeks.[18]

While the bulk of the data suggest that delaying adjuvant therapy more than 6 weeks from the time of surgery may be detrimental,[15] there appears to be no benefit or detriment to delaying standard chemoradiation therapy within the 6-week timeframe that is typically observed in most clinical trials.

Our present study is valuable as it analyzes patients eligible for treatment on large, randomized clinical trials in settings comparable to those in which patients received first-line radiation as monotherapy, reported in our first publication. The number of patients studied, 1395, comprises a much larger database than for any of the recent studies, which is relevant for the statistical conclusions that can be made from the analyses. Additionally, more than 80% of the patients in our analysis had MGMT status determined, which lends credence to the survival results. Tumors with methylation of the promoter region of MGMT (methylated MGMT) are known to have the greatest magnitude of benefit from the combined chemoradiation treatment, with an impressive 2-year survival rate of 50% for this molecularly sensitive group.[19]

A lower (more favorable) RPA class was found by multivariate analysis to be a predictive factor for improved survival in this current study, as was the case in our prior paper (Tables 3 and 4).

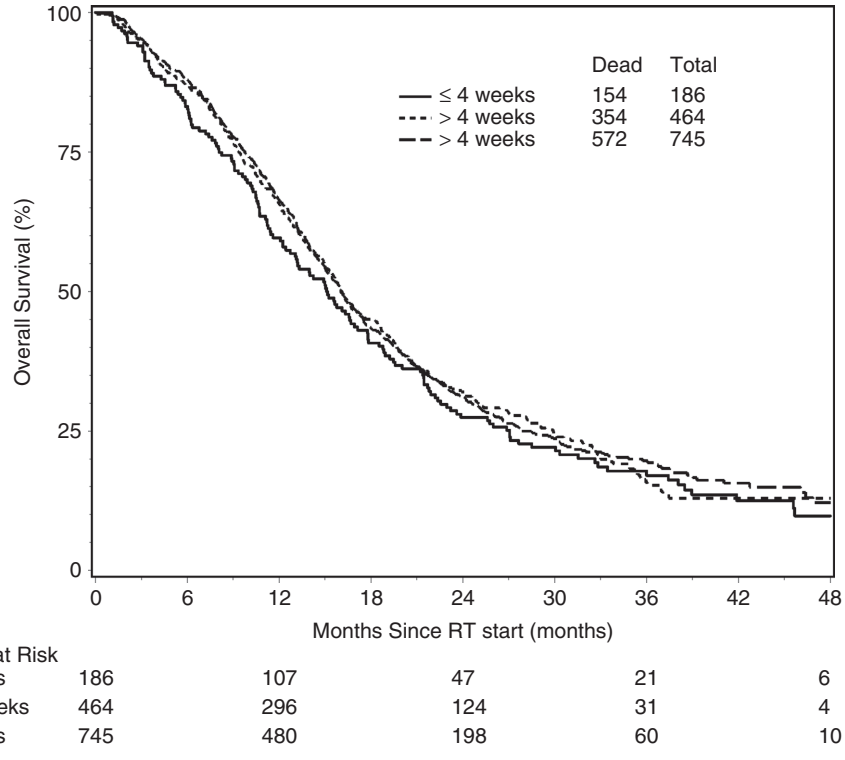

Fig. 2 Overall survival by 3 interval groups.

Table 4 Recent studies reporting impact of RT-delay for RT/chemo-RT in newly diagnosed glioblastoma (all studies other than Blumenthal 2009 involved chemo-RT)

Author	Type of Study	No. of Pts	Delay	Multivariate Analysis Significant Factors for OS	MGMT	Impact of Delay
Current study, Blumenthal 2016	NRG Oncology/RTOG retrospective analysis of 2 studies in the RT/TMZ era	1395	≤4 vs >4 (up to 6) wk delay.* Most patients were treated between 3 and 5 wk	RPA stage, MGMT status	Known in 80% of pts	None
Blumenthal 2009	RTOG retrospective analysis 1974–2003 of 16 *single agent RT* trials	2855	≤2 vs >4 (up to 6) wk delay	RPA stage; RT delay >4 wk	Not known	Advantage (OS) for delaying RT up to 6 wk: 12.5 mo vs 9.2 mo ($P < 0.0001$)
Noel 2012	French multicenter (18) 2006	282	Median 41 d	Age, type of surgery	Not known	None
Spratt 2014	Memorial Sloan-Kettering Cancer Center 2000–2012	345	≤2, 2–5, and ≥6 wk		Known in 45.8%	Detrimental to OS if delay >6 wk
Hans 2015	University of San Francisco: 4 clinical trials 2004–2010	198	<30 d vs 30–34 d post-op	KPS, extent of resection	Not available	Advantage for PFS and OS if delayed 30–34 d (not >34 d)
Adeberg 2015	Heidelberg, retrospective	50	While awaiting MGMT results (~1 wk)	MGMT	Known in all study cases, and 25% of the reference group	Decreased survival (PFS and OS) if treatment begun earlier than 24 d
Sun 2015	The Cancer Genome Atlas	218	Median delay 27 d; examined per quartiles (<20; 21–27 d; 28–35; >36 d)	Age	Not known	None* (up to 6 wk; worse OS >6 wk)
Louvel 2016	French multicenter	692	Median 1.5 mo	Female sex, total/subtotal resection; RPA stage	Not examined	None

Pretreatment factors, including the volume of tumor treated, the exact dose delivered, and posttreatment sequelae/toxicities, were not analyzed and as such may limit the study results and implications; however, strengths of this analysis include central review of treatment fields and protocol dose conformity quality assurance, which were performed on the initial clinical study cohorts as required by RTOG/NRG standards.

Both of the randomized studies inherently restricted the window of treatment initiation: in RTOG 0525, treatment needed to be initiated by <5 weeks from the time of surgery, and in RTOG 0825, within the narrow window of 3–5 weeks postoperatively. Due to the limited number of outlying patients who were treated at <3 weeks or >5 weeks from the time of surgery, we changed our prospectively designed analysis post hoc, from 3 time intervals (planned to correspond more directly to our previously published work): ≤3 weeks, >3–4 weeks, and >4 weeks to 2 groups: >4 and ≤4 weeks, based on the median timepoint between surgery and initiation of chemoradiation of 4 weeks. As such, the implications for generalization to patients in the community starting earlier or later than this time period may be limited.

Conclusion

Delaying the initiation of concurrent TMZ and radiation for the treatment of newly diagnosed GBM is not detrimental within the accepted guidelines of the 5–6 weeks postoperative period.

Supplementary Material

Supplementary material is available at *Neuro-Oncology* online

Funding

This project was supported by grants U10CA180868 (NRG Oncology Operations) and U10CA180822 (NRG Oncology SDMC) from the National Cancer Institute (NCI) and Genentech. This project is also funded, in part, under a grant from the Pennsylvania Department of Health. The Department specifically disclaims responsibility for any analyses, interpretations, or conclusions.

Acknowledgment

We would like to acknowledge Sesalie L Smathers, MD of the Southeast Cancer Control Consortium, Inc, CCOP, Asheville, North Carolina, for her contribution to this study. This paper was presented in abstract form at SNO 2015, #0237

Conflict of interest statement. The authors declare no conflict of interest.

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