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Impact of Timing of Concurrent Chemoradiation for Newly Diagnosed Glioblastoma: A Critical Review of Current Evidence

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Glioblastoma (GBM) is the most common primary malignant brain tumor in adults, and it remains a very challenging disease. Despite advances in modern surgical and adjuvant therapies, the prognosis remains poor with a median overall survival (OS) of <2 years. The current standard therapy, as established by the European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada (EORTC/NCIC) phase 3 trial, includes maximal safe surgical resection followed by external beam radiation therapy at 60 Gy with concurrent daily temozolomide (TMZ) followed by adjuvant TMZ.[1]

With aggressive malignancies such as GBM, minimizing the delay in initiating cytotoxic therapies is a widely held management goal. Any delay in beginning adjuvant therapy may represent a significant source of anxiety for patients and providers because of the presumed association with inferior tumor control. GBM is an extremely aggressive disease with a rapid doubling time, estimated to be only 24 days.[2,3] In addition, there is evidence of decreased tumor control with radiotherapy for larger tumors, and it seems intuitive that delays in initiating postoperative radiation therapy will lead to worse patient outcomes.[4] The effect of radiotherapy timing on outcome has been evaluated across multiple types of malignancies such as breast,[5,6] lung,[7] and head and neck cancers.[8,9] These studies consistently demonstrate higher recurrence rates and worse outcomes associated with delayed administration of adjuvant radiotherapy. However, in the context of GBM and high-grade gliomas, the relationship between delayed radiotherapy and clinical outcome remains less clear, with studies in the published literature showing conflicting results. Here, we review the results of studies examining the impact of time to initiating postoperative radiotherapy and our experience on the topic (Table 1).

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The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

PUBLISHED LITERATURE

Studies Demonstrating Negative the Impact of Delays in Adjuvant Radiotherapy

Three retrospective studies have reported that delays in receiving adjuvant radiotherapy were associated with decreased survival in GBM patients.[10–12] In a multivariate analysis of 182 patients, Do et al[10] demonstrated that factors associated with worse OS included older age, reduced radiation dose, and prolonged waiting times from clinical presentation to radiotherapy. Interestingly, the authors estimated a 2% increase in risk of death for each day that radiotherapy was delayed; however, the time from surgical resection to radiotherapy was not associated with poor OS. This suggests that the time between initial presentation and radiotherapy may have more of an impact on OS than the interval between resection and radiation.

In a series of 172 patients with high-grade gliomas, Irwin et al[11] found time between surgery and radiotherapy to be an independent predictor of shorter survival such that the risk of death increased 1.2% per day of delay between surgery and radiotherapy. Their results remained significant while accounting for other prognostic variables such as age, grade, performance status, radiotherapy dose, and extent of surgery in a multivariate analysis. These findings suggest that an 8-week waiting period reduced the median OS by 11 weeks compared with a 2-week wait for a typical patient.[11]

In a series of 308 patients with high-grade gliomas, Glinski et al[12] also studied the impact of the interval between surgery and initiation of radiation therapy on OS, using a multivariate analysis accounting for age, sex, Karnofsky Performance Status Scale score, extent of resection, grade, and tumor location. The authors discovered that delay beyond 37 days after surgery, the median in their series, was associated with a significantly worse OS.

Studies Showing No Association Between Timing of Adjuvant Radiotherapy and Outcomes

In a series of 400 patients with GBM, Noel et al[13] found that timing did not significantly affect OS, even in multivariate analysis. In a study of 149 patients, Lutterbach et al[14] also demonstrated no statistically significant association in multivariate analysis between intervals from surgery to radiotherapy and survival outcomes. Similar results were reported by Hulshof et al,[15] who examined 198 patients with GBM.

Lai et al[16] studied a cohort of 1375 patients from the Surveillance, Epidemiology, and End Results (SEER) database and observed that an interval from surgery to radiation of >22 days was associated with worse OS in univariate analysis. However, after adjustment for other prognostic variables in multivariate analysis, the interval from surgery to radiotherapy was no longer a statistically significant variable in the final model.[16]

Studies Showing Possible Benefit of Delay in Initiation of Radiation

The largest series to date analyzing the impact of timing of adjuvant radiotherapy for GBM was a secondary analysis by Blumenthal and colleagues[17] of 16 Radiation Therapy Oncology Group studies including >2800 patients. Interestingly, the authors observed a modest improvement in OS with delay of radiotherapy up to and beyond 4 weeks after

surgical resection. Wehming et al,[18] in a series of 153 patients, observed that a longer interval from surgery to radiotherapy was associated with improved progression-free survival (PFS) and OS on univariate analysis; however, time interval was no longer a significant factor after multivariate analysis.

Authors' Experience

We have recently analyzed results from 4 clinical trials conducted at the University of California, San Francisco (Han SJ, Rutledge WC, Molinaro AM, et al. The effect of timing of concurrent chemoradiation in patients with newly diagnosed glioblastoma. *Neurosurgery*. In press.). Our study included 198 adult patients with newly diagnosed supratentorial GBM who between 2004 and 2010 enrolled in 4 clinical trials consisting of radiation plus TMZ and an experimental agent (Table 2).[19–22] The interval to initiation of therapy was defined from the time of surgical resection. The partitioning deletion/substitution/addition algorithm was used to determine the cutoff points for timing of chemoradiation at which there was a significant difference in OS and PFS.[23] The partitioning deletion/substitution/addition algorithm was developed for use in cancer survival analyses that use multiple predictive variables and their interactions. The algorithm chooses the best among all "or" scenarios of variables while allowing for both continuous and categorical variables in the model. Median wait time between surgery and initiation of concurrent chemoradiation was 29.5 days (range, 7–56 days). A short delay in chemoradiation administration (at 30–34 days) was predictive of prolonged OS (HR = 0.63; $P = .03$) and prolonged PFS (HR = 0.68; $P = .06$) compared with early initiation of concurrent chemoradiation (<30 days). These results included adjustment for protocol and baseline prognostic variables, including extent of resection, by multivariate analysis. A delay to chemoradiation beyond 34 days was not associated with improved OS or PFS compared with early initiation (HR = 0.94, $P = .77$; and HR = 0.91, $P = .63$, respectively). Our results support those found by Blumenthal et al[17] that a modest delay to initiation of radiotherapy of approximately 4 weeks (28 days in their analysis and 30 days in ours) was associated with improved survival outcomes.

Potential Role of Concurrent TMZ With Radiotherapy

The majority of studies discussed above were completed before the establishment of concurrent TMZ as standard therapy for newly diagnosed GBM patients, raising the question of whether these results remain relevant in the modern era of concurrent chemoradiation for GBM. The series reported by Do et al,[10] Lutterbach et al,[14] and Irwin et al[11] were completed in an era before TMZ, and information on chemotherapeutics is not provided in the studies by Glinski et al[12] and Hulshof et al.[15] In the cohorts of Lai et al[16] and Wehming et al,[18] a significant portion of patients received adjuvant chemotherapy, and the use of chemotherapy was included in their multivariate analyses, but it is not stated whether any of these agents included TMZ.

In the series by Noel et al,[13] a subgroup of 229 patients received radiation with concurrent and adjuvant TMZ. Among both cohorts who did and did not receive concurrent TMZ, there was no significant relationship observed between timing of radiotherapy initiation and outcome. To the best of our knowledge, there is only 1 series in which the entire cohort universally received radiotherapy with concurrent and adjuvant TMZ as established by the

EORTC/NCIC phase 3 trial.[1] Contrary to results from the subgroup receiving concurrent and adjuvant TMZ in the Noel et al series, our results revealed that a short delay in initiating radiotherapy may have beneficial results. However, in our experience, it is difficult to distinguish whether the effects of chemoradiation timing on outcome are more closely related to the timing of radiotherapy or TMZ administration.

Mathematical modeling studies of tumor responses to radiotherapy and TMZ suggest that TMZ given concomitantly with radiotherapy synergistically enhances the radiosensitivity of GBM.[24] In 1 study of patients with newly diagnosed GBM, administration of TMZ before radiotherapy resulted in inferior survival outcomes compared with administration of TMZ concomitantly with radiation; however, it remains unclear how much impact the large delay of radiotherapy (up to 4 months for the cohort receiving radiotherapy followed by TMZ) had on the survival outcomes.[25] Along similar lines, regimens of concurrent radiation and chemotherapy with carmustine and sequential radiotherapy followed by carmustine had equivalent survival outcomes.[26] These 2 studies appear to suggest a greater potential impact of adjuvant radiotherapy timing in GBM treatment.

Baseline Prognostic Factors in Patients Receiving Early Adjuvant Therapy

Interestingly, in their univariate model, Lai et al[16] initially found improved survival with delay of >22 days from surgery to radiotherapy; however, waiting time was no longer a significant predictor of survival after adjustment for other prognostic variables. Their findings highlight a possible source of confounding also recognized by Blumenthal et al[17] and Noel et al[13]: Treating physicians may start adjuvant therapy earlier in patients they are more concerned about, leading to an association between shorter waiting times and poor prognostic factors such as older age, worse Karnofsky Performance Status Scale, or incomplete extent of resection at surgery. This phenomenon was observed to various degrees in prior reports and in our series. In our experience, patients with shortest delay (<30 days) to chemoradiation tended to be older and were more likely to have undergone a subtotal resection or biopsy. However, this factor alone does not reconcile the discrepancies in the published literature because delay to therapy remained a significant outcome predictor even after adjustment for known confounding prognostic factors in studies by Blumenthal et al,[17] Noel et al,[13] Irwin et al,[11] and Do et al,[10] as well as in our series.

Potential Explanation for Discrepant Findings

In addition to varying chemotherapeutic regimens across different studies, particularly in the use of concurrent TMZ, it is important to consider the varying spectrum of wait times among the patients studied. Blumenthal et al[17] suspected that waiting >6 weeks was not beneficial, which is consistent with our experience. Patients studied by Do et al[10] had delays as long as 62 days, and half of the Irwin et al[11] cohort started radiation after 5 weeks whereas some waited as long as 15 weeks. In the series by Glinski et al,[12] the median delay to radiotherapy was 37 days. Thus, the potentially detrimental impact of delayed radiotherapy initiation may have affected only a subset of patients in these cohorts. Although we found no deleterious effects associated with waiting times beyond 34 days compared with short waiting times (<30 days), it remains possible that shorter survival may be encountered if this delay is even longer, as demonstrated by Irwin et al.[11]

It is worth noting that some of the studies we reviewed included both grade 3 and 4 high-grade gliomas, whereas others included only patients with GBM. Interestingly, 3 of the 4 published series that included both grade 3 and 4 tumors were the 3 reports that cited worse survival outcome with delays to radiotherapy.[10–12] Although tumor grade was included in their respective multivariate analyses, it may have been interesting to see outcomes disaggregated by tumor grade in these patient cohorts.

Differences in statistical methods used may also have contributed to the varying results described in the literature. Most studies dichotomized timing as a binary variable, using the median length of delay in the cohort as the cutoff threshold.[12–14,18] Other studies modeled timing in categories using quartiles or percentiles,[15–17] and 2 studies considered length of delay a continuous variable in weeks.[10,11] Our analysis was unique in its use of the partitioning deletion/substitution/addition method, which allowed the data to dictate the cutoffs in timing to initiation of therapy. This method is likely more sensitive to the potential effects of waiting time on outcome, whereas the use of percentiles (as in the Noel et al[13] analysis) may fail to detect effects of a smaller magnitude. However, there is the possibility of overfitting in our model, and validation in an external cohort is warranted.

Given the aggressive nature of GBM, it is easy to postulate why long delays in adjuvant radiation may lead to less favorable outcomes. On the contrary, radiation given too early after the initial insult of surgical resection may also have detrimental effects. One mechanistic hypothesis states that hypoxia and edema of the surgical bed resulting from resection may diminish the radiosensitivity of the tissue.[17] Shrinking of the tumor cavity can also be seen up to 4 weeks, which suggests the need for larger radiation field sizes and hence greater potential for radiation-induced injury with earlier postoperative radiotherapy.[27] This phenomenon has been demonstrated in rat models, showing higher levels of brain injury with early postoperative initiation of radiation.[28]

LIMITATIONS

The goals of the present review are to summarize the experiences of our own practice with regard to chemoradiation timing in GBM treatment and to provide an overview of the literature. However, the limitation of this review is that we did not perform a formal meta-analysis of the literature. Thus, our discussion is prone to bias, particularly with regard to treatment experiences in our own patient population, which may differ from patient populations at other centers. In addition, all studies reviewed here are retrospective in nature and thus are subject to the bias inherent to retrospective studies. Nevertheless, this approach provides a discussion of practice patterns at a high-volume neuro-oncology center that practitioners at other institutions may find useful and a representative overview of the relevant literature.

CONCLUSION

To date, the current evidence on the impact of timing of radiotherapy or concurrent chemoradiation remains exclusively retrospective in nature. A prospective randomized trial designed to study these potential effects would be challenging because of issues of ethics

and clinical equipoise. Our as-yet-unpublished experience described in this article represents the second large study to demonstrate a clear clinical benefit associated with a short delay in the initiation of adjuvant radiotherapy and the first to demonstrate improved outcomes associated with a short delay in concurrent chemoradiation with TMZ. Although we caution against universal deliberate delay of concurrent chemoradiation, these results may have implications for clinical trial entry. Minimizing the degree of heterogeneity in initiation times for inclusion into clinical trials should be encouraged.

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ABBREVIATIONS

EORTC/NCIC	European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada
GBM	glioblastoma
OS	overall survival
PFS	progression-free survival
SEER	Surveillance, Epidemiology, and End Results
TMZ	temozolomide

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TABLE 1

Reports Studying Potential Impact of Timing to Radiation[a]

Authors, Year of Publication	n	GBM, %	Median Interval From Surgery to Radiation	Chemotherapy	Patients Who Received Concurrent and Adjuvant TMZ, %	Effect of Timing to Radiotherapy
Studies supporting negative impact of delay to radiation on outcome						
Do et al,[10] 2000	182	65	26 d	No	None	Risk of death increased by 2% for each day of waiting from presentation to RT
Irwin et al,[11] 2007	172	84	35 d	No	None	Risk of death increased by 1.2% for each day of waiting from surgery to RT
Glinski et al,[12] 2012	308	64	37 d	Not reported	Not reported	HR, 1.54 for interval from surgery to RT >37 d
Studies showing no impact of timing to radiation on outcome						
Noel et al,[13] 2012	400	100	41 d	229 patients received concurrent and adjuvant TMZ	57	Waiting time until radiotherapy did not affect survival outcomes
Lutterbach et al,[14] 1999	149	100	13 d	No	None	Waiting time until radiotherapy did not affect survival outcomes
Hulshof et al,[15] 2001	198	100	30 d	Not reported	Not reported	Waiting time until radiotherapy did not affect survival outcomes
Lai et al,[16] 2010	1,375	100	15 d	Some chemotherapy given in 27% of patients	Not reported	Waiting time of >22 d showed significant inverse relationship with survival but was not significant in multivariate analysis
Studies supporting potential benefit of modest delay to radiation						
Blumenthal et al,[17] 2009	2,855	100	3 wk	Many included trials studied concurrent and adjuvant chemotherapeutics; exact proportion	Some, exact proportion not reported	Waiting for RT >4 wk from surgery was associated with significantly improved survival

Authors, Year of Publication	n	GBM, %	Median Interval From Surgery to Radiation	Chemotherapy	Patients Who Received Concurrent and Adjuvant TMZ, %	Effect of Timing to Radiotherapy
				not reported		
Wehming et al,[18] 2012	153	70	24 d	70 patients received TMZ, exact regimen not reported	46 received TMZ but it is unknown whether this regimen was concurrent and adjuvant	Delay >24 d from surgery to RT was associated with improved survival but was not significant in multivariate analysis
Authors' experience	198	100	29.5 d	All patients received concurrent and adjuvant TMZ	100	Short delay in chemoradiation initiation at 30–34 d was associated with prolonged OS and PFS

[a]GBM, glioblastoma; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; TMZ, temozolomide.

TABLE 2

Baseline Characteristics of Patients Included in the Authors' Experience[a]

	Interval From Surgery to Initiation of Radiation			
	<30 d (n = 100)	**30–34 d (n = 48)**	**>34 d (n = 50)**	***P***
Age, median, y	56.4	51.3	57.8	.02
Age, range, y	27.3–80.0	22.6–72.9	21.3–74.3	
KPS score, n (%)				.61
60	3 (3)	1 (2)	1 (2)	
70	3 (3)	2 (4)	0 (0)	
80	18 (18)	9 (19)	8 (16)	
90	73 (73)	33 (69)	39 (78)	
100	3 (3)	3 (6)	2 (4)	
Experimental regimen, n (%)				.08
Erlotinib + TMZ	37 (37)	14 (29)	14 (28)	
Enzastaurin + TMZ	37 (37)	11 (23)	20 (40)	
Erlotinib + Bev + TMZ	26 (26)	23 (48)	16 (32)	
Extent of resection, %				.006
Biopsy	26 (26)	2 (4)	5 (10)	
STR	40 (40)	26 (54)	29 (59)	
GTR	33 (3)	19 (40)	15 (31)	

[a]Bev, bevacizumab; GTR, gross total resection; KPS, Karnofsky Performance Status Scale; STR, subtotal resection; TMZ, temozolomide. Variables included in the multivariate analysis included age, KPS, experimental regimen, extent of resection, and time to radiation.