Newly diagnosed glioblastoma: adverse socioeconomic factors correlate with delay in radiotherapy initiation and worse overall survival

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ABSTRACT

The optimal time for starting radiation in patients with glioblastoma (GBM) is controversial. We aimed to evaluate postoperative radiotherapy treatment patterns and the impact of timing of radiotherapy on survival outcomes in patients with GBM using a large, national hospital-based registry in the era of Stupp chemoradiation. We performed a retrospective cohort study using the National Cancer Data Base and identified adults with GBM diagnosed between 2010 and 2013 and treated with chemoradiation. We classified time from surgery/biopsy to radiation start into the following categories: <15 days, 15–21 days, 22–28 days, 29–35 days, 36–42 days and >42 days. We assessed the relation between time to radiation start and survival using Cox proportional hazards modeling adjusting for clinically relevant variables that were selected a priori. We used multivariate logistic modeling to determine factors independently associated with receipt of delayed radiation treatment. A total of 12,738 patients met our inclusion criteria after our cohort selection process. The majority of patients underwent either gross total (n = 5270, 41%) or subtotal (n = 4700, 37%) resection, while 2768 patients (22%) underwent biopsy only. Median time from definitive surgery or biopsy to initiation of radiation was 29 days (interquartile range 24–36 days). For patients who had biopsy or subtotal resection, earlier initiation of radiation did not appear to be associated with improved survival. However, among patients who underwent gross total resection, there appeared to be improved survival with early initiation of radiation. Patients who initiated radiation within 15–21 days of gross total resection had improved survival (hazard ratio 0.82, 95% confidence interval 0.69–0.98, P = 0.03) compared with patients who had delayed (>42 days after surgery) radiation. There was also a trend (P = 0.07 to 0.12) for improved survival for patients who initiated radiation within 22–35 days of gross total resection compared with patients who had delayed radiation. Patients who were black, had Medicaid or other government insurance or were not insured, and who lived in metropolitan areas or further away from the treating facility had higher odds of receiving radiation >35 days after gross total resection. Patients who lived in higher income areas had higher odds of receiving radiation within 35 days of a gross total resection. In a large cohort of patients with GBM treated with chemoradiation, our data suggest a survival benefit in initiating radiotherapy within 35 days after gross total resection compared with patients who had delayed radiation. Further research is warranted to understand barriers to timely access to optimal therapy.

Keywords: glioblastoma; chemoradiation; treatment timing

INTRODUCTION

Survival outcomes are poor for patients diagnosed with glioblastoma (GBM), despite standard of care therapies, including surgery, radiotherapy and temozolomide. There has been continued effort to optimize the delivery of radiotherapy in these patients in order to improve outcomes. For many cancers, including breast and head
and neck histologies, delay in initiation of radiotherapy has been associated with worse local control and survival outcomes [1]. Patients with rapidly growing tumors such as GBMs are potentially most at risk of the negative consequences of treatment delay [2].

However, the optimal time to start radiation in patients with GBM is controversial. Although some institutional, retrospective series have shown an adverse impact on survival with radiation delay after surgery, others have shown no impact [3–7]. A secondary analysis of the Radiation Therapy Oncology Group database of patients with glioblastoma showed no evidence of worse survival in delaying initiation of radiation for up to 6 weeks and, interestingly, superior survival in patients for whom radiation was delayed beyond 4 weeks from surgery [3]. Selection bias may explain these retrospective findings of survival detriment with early initiation of radiation: patients with the most adverse characteristics are likely the ones for whom physicians started radiation sooner. Additionally, small numbers of patients and heterogeneous, outdated therapies used in many of these studies make interpretation of the results challenging.

To address the limitations of these prior studies, we aimed to evaluate postoperative radiotherapy treatment patterns and the impact of timing of radiotherapy on survival outcomes in patients with glioblastoma using a large, national hospital-based registry, in the era of Stupp chemoradiation [8].

**MATERIALS AND METHODS**

**Database and cohort selection**

The National Cancer Database (NCDB) is a joint program of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. It is a hospital-based registry that collects data from more than 1500 CoC-accredited cancer hospitals and contains detailed information, including demographics, disease stage, comorbidity, radiation, surgery, and chemotherapy delivered during the first course of treatment on 70% of all incident cancer cases in the USA. The American College of Surgeons and the CoC have not verified and are not responsible for the analytic or statistical methodology used or for the conclusions drawn from these data by the investigator. The following NCDB analysis was performed with the approval of our institutional review board.

We queried the NCDB 2014 Participant User File for adult patients with primary glioblastoma using the International Classification of Diseases for Oncology histology code 9440 and site-specific codes C720–3, and included only patients with WHO Grade IV disease. We included patients diagnosed between 2010 and 2013 to ensure adequate follow-up and vital status information, and because site-specific factors such as extent of resection were consistently available beginning in 2010. We included patients who received radiation and chemotherapy within 60 days of surgery to minimize the inclusion of patients who received treatment for progressive disease. To address immortal time bias, we excluded patients who died or were lost to follow-up during the 60 day time interval after surgery. We required patients to have a known date of definitive surgery or biopsy and radiation start (See Table 1 for cohort selection).

**Table 1. Cohort selection**

| Description | No. | % |
|-------------|-----|---|
| Patients with primary glioblastoma diagnosed 2010–2013 | 38 694 | 100.0% |
| Exclude patients where diagnosis dates precede reference dates to ensure data completeness | 38 515 | 99.5% |
| Limit to patients where glioblastoma diagnosis is first cancer diagnosis | 33 430 | 86.4% |
| Limit to patients 18 years or older | 33 092 | 85.5% |
| Required to have known vital status | 33 092 | 85.5% |
| All patients need to have known date of definitive surgery or biopsy; exclude patients who were diagnosed at autopsy or with extent of resection unknown | 22 313 | 57.7% |
| All patients need to have both radiation and chemotherapy within 60 days of surgery | 15 522 | 40.1% |
| Restrict to patients who received adjuvant chemotherapy | 13 048 | 33.7% |
| Exclude patients who died or lost follow-up within 60 days of surgery | 12 859 | 33.2% |
| Exclude patients where cases diagnosed at reporting facility did not receive any treatment at that facility | 12 738 | 32.9% |

**Covariates**

We included relevant patient, tumor and treatment characteristics from the database in our analysis. Patient comorbidities were categorized as 0, 1 or 2 according to the Charlson–Deyo comorbidity score [9]. Distance from facility was based on the ‘great circle’ distance in miles between the patient’s residence and the hospital that reported the case, and was dichotomized into categories of ≤50 miles and >50 miles [10]. Residence (metropolitan, urban, or rural) was coded according to published files by the US Department of Agriculture Economic Research Service. Median household income for each patient’s zip code of residence was derived from 2012 US Census data. Reporting facilities were assigned a category classification by the CoC program. Time from definitive surgery or biopsy to radiation initiation was categorized into quartiles.

**Statistical analysis**

Pearson chi-square tests were used to assess associations between baseline characteristics and age groups. Our primary outcome was overall survival. Survival time was defined as time from definitive surgery or biopsy to date of death or last follow-up. We assessed the relation between time from surgery to radiation initiation and all-cause mortality using Cox proportional hazard modeling. We included in our adjusted models relevant patient, tumor and treatment covariates (age, gender, race, comorbidity score, year of...
diagnosis, patient distance from reporting facility, zip code income, radiation dose, insurance type, and urban/metro/rural residence) that were selected \textit{a priori} based on clinical judgment. In order to identify the optimal time from surgery/biopsy to radiation start, we classified time into the following categories: <15 days, 15–21 days, 22–28 days, 29–35 days, 36–42 days and >42 days.

Because facility type and region of the country are suppressed in the NCDB for patients younger than 40 years, we did not include these variables in our main multivariate models. Instead, we stratified our models on facility as there may be different institutional practices with regard to starting radiation. We performed sensitivity analyses in which we additionally adjusted for facility type and region of the country.

We used multivariate logistic modeling to determine factors independently associated with receipt of delayed radiation treatment. We initially included the same patient and tumor characteristics as above, and used a reverse, stepwise selection process to construct a working model, retaining variables with $P < 0.1$.

All tests were 2-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SAS Enterprise Guide (version 7.12, SAS Institute, Cary, North Carolina).

**RESULTS**

**Patient and treatment characteristics**

Table 1 shows that a total of 12,738 patients met our inclusion criteria after our cohort selection process. The majority of patients underwent either gross total (n = 5270, 41%) or subtotal (n = 4700, 37%) resection, while 2768 patients (22%) underwent biopsy only. The majority of patients received 60 Gy or higher of adjuvant radiation (n = 8461, 66%). The median time from definitive surgery or biopsy and initiation of radiation was 29 days (interquartile range 24–36 days). Figure 1 shows the distribution of time to radiation initiation by extent of resection in our entire cohort.

Table 2 shows baseline patient and treatment characteristics by extent of resection for our entire cohort. Patients who resided in lower income areas, had Medicare/government insurance or no insurance, and had higher comorbidity scores were less likely to undergo gross total resection. White patients and patients treated at integrated network cancer programs were more likely to undergo gross total resection.

**Association between time to radiation initiation and survival**

The median survival times (conditional on having survived 2 months as required for inclusion in this study) for those who had biopsy only, subtotal resection, and gross total resection were 14.2 months [95% confidence interval (CI) 13.6–14.8], 14.3 months (95% CI 14.0–14.7) and 17.8 months (95% CI 17.4–18.3), respectively (log-rank $P < 0.0001$).

We examined the impact of time to radiation initiation and survival, stratified by extent of surgery due to a significant interaction ($P < 0.0001$) between extent of surgery and time to radiation initiation that we found in our survival models. Table 3 shows the results of our adjusted models.

For patients who had biopsy or subtotal resection, earlier initiation of radiation did not appear to be associated with improved survival. In fact, among patients who underwent biopsy only, there was significantly worse survival (hazard ratio 1.67, 95% CI 1.24–2.25, $P = 0.0007$) with earlier initiation of radiation (within 15 days of biopsy) compared with delayed radiation (defined as >42 days after surgery or biopsy). However, among patients who underwent gross total resection, there appeared to be improved survival with early initiation of radiation. Patients who initiated radiation within 15–21 days of gross total resection had improved survival compared to those who initiated radiation after 22–28 days of gross total resection.

![Fig. 1. Distribution of time to radiation initiation from date of biopsy/surgery by extent of resection in entire study cohort.](image-url)
Table 2. Baseline patient and treatment characteristics by extent of surgery

|                              | Total patients | Biopsy only | Subtotal resection | Gross total resection | P value<sup>a</sup> |
|------------------------------|----------------|-------------|--------------------|-----------------------|---------------------|
|                              |                | 2768        | 4700               | 5270                  |                     |
| Age                          |                |             |                    |                       | 0.33                |
| 50 years or younger          |                |             |                    |                       |                     |
| 51–60 years                  |                |             |                    |                       |                     |
| 61–69 years                  |                |             |                    |                       |                     |
| 70 years or older            |                |             |                    |                       |                     |
| Gender                       |                |             |                    |                       | 0.05                |
| Male                         |                |             |                    |                       |                     |
| Female                       |                |             |                    |                       |                     |
| Race                         |                |             |                    |                       | 0.003               |
| White                        |                |             |                    |                       |                     |
| Black                        |                |             |                    |                       |                     |
| Other                        |                |             |                    |                       |                     |
| Year of diagnosis            |                |             |                    |                       | <0.0001             |
| 2010                         |                |             |                    |                       |                     |
| 2011                         |                |             |                    |                       |                     |
| 2012                         |                |             |                    |                       |                     |
| 2013                         |                |             |                    |                       |                     |
| Comorbidity score            |                |             |                    |                       | 0.0006              |
| 0                            |                |             |                    |                       |                     |
| 1                            |                |             |                    |                       |                     |
| 2 or higher                  |                |             |                    |                       |                     |
| Location<sup>b</sup>         |                |             |                    |                       | <0.0001             |
| Northeast                    |                |             |                    |                       |                     |
| South                        |                |             |                    |                       |                     |
| Central                      |                |             |                    |                       |                     |
| West                         |                |             |                    |                       |                     |
| Unknown                      |                |             |                    |                       |                     |
| Facility type<sup>b</sup>    |                |             |                    |                       | 0.002               |
| Community cancer program     |                |             |                    |                       |                     |
| Comprehensive community cancer program | |             |                    |                       |                     |
| Academic/Research program    |                |             |                    |                       |                     |
| Integrated network cancer program |         |             |                    |                       |                     |

Continued
survival (hazard ratio 0.82, 95% CI 0.69–0.98, \( P = 0.03 \)) compared with patients who had delayed radiation. There was also a trend \( (P = 0.07–0.12) \) for improved survival for patients who initiated radiation within 22–35 days of gross total resection compared with patients who had delayed radiation.

### Factors associated with delayed radiation after gross total resection

Using 35 days as a cut-off based on our Table 3 results, we then looked at factors that were independently associated with receiving radiation >35 days after gross total resection (Table 4). Patients who were black, had Medicaid or other government insurance or were not insured, and who lived in metropolitan areas or further away from the treating facility had higher odds of receiving radiation >35 days after gross total resection. Patients who lived in higher income areas had lower odds of receiving radiation >35 days after gross total resection.

### Sensitivity analyses

We performed sensitivity analyses adjusting for facility type and region of the country (available for patients 40 years and older), and found that our results were materially unchanged. Patients who
initiated radiation within 15–21 days of gross total resection had improved survival (hazard ratio 0.80, 95% CI 0.66–0.95, \( P = 0.01 \)) compared with patients who had delayed radiation. There continued to be a trend for improved survival for patients who initiated radiation within 22–35 days of gross total resection compared with patients who initiated radiation after 35 days of gross total resection (data not shown).

**DISCUSSION**

Using a large, nationally representative sample of patients with glioblastoma treated with chemotherapy and radiation, we found that there may be a survival benefit with earlier initiation of radiation after gross total resection. However, there appeared to be no such association for patients who received subtotal resection and biopsy only, and even possible survival detriment associated with early initiation of radiation after biopsy only.

Others have reported findings of increased survival with earlier initiation of radiation treatment for patients with Grade III or IV gliomas in the pre-temozolomide era. Do et al. found a 2% increased risk of death for each additional day after presentation before initiation of radiation \([4]\). Irwin et al. similarly reported a 9% increased risk of death per week of delay \([5]\). More modern series of patients with glioblastoma treated with both adjuvant chemotherapy and radiotherapy found that starting radiation within 42 days of surgery was associated with improved progression-free and/or overall survival \([8, 11, 12]\). Corroborating our data, Valduvieco et al. analyzed only patients who had gross total resection and found improved survival with earlier initiation of radiation \([13]\). Given the short doubling time of GBM \([14]\), it is intuitive that timely access to radiation treatment may result in improved outcomes.

However, multiple other studies have shown that time to radiation start has no association with survival outcomes \([3, 6, 7, 15]\). Blumenthal et al. included thousands of GBM patients treated on Radiation Therapy Oncology Group (RTOG) trials in their analysis, and found significantly better, rather than inferior, survival with a wait time to radiation start of more than 4 weeks (but less than 6 weeks) \([3]\). There are several possible explanations for the unexpected finding of inferior outcomes with earlier initiation of radiation. Experimental animal data suggests that early delivery of radiation after surgery may result in higher levels of brain tissue damage \([16]\). Postsurgical hypoxia and edema in the immediate

### Table 3. Association between various cut-points for time from surgery/biopsy and radiation start and survival

| Time Post Procedure | Biopsy only Adjusted Hazard Ratio | 95% CI | \( P \) | Subtotal resection Adjusted Hazard Ratio | 95% CI | \( P \) | Gross total resection Adjusted Hazard Ratio | 95% CI | \( P \) |
|---------------------|----------------------------------|-------|-----|----------------------------------|-------|-----|----------------------------------|-------|-----|
| <15 days            | 1.67                             | 1.24–2.25 | 0.0007 | 1.12                             | 0.86–1.46 | 0.39 | 1.17                             | 0.88–1.56 | 0.29 |
| 15–21 days          | 1.11                             | 0.88–1.40 | 0.39  | 1.11                             | 0.93–1.13 | 0.26 | 0.82                             | 0.69–0.98 | 0.03 |
| 22–28 days          | 0.96                             | 0.77–1.19 | 0.69  | 0.94                             | 0.80–1.09 | 0.40 | 0.89                             | 0.77–1.03 | 0.12 |
| 29–35 days          | 0.94                             | 0.76–1.17 | 0.58  | 0.94                             | 0.80–1.09 | 0.40 | 0.88                             | 0.76–1.01 | 0.07 |
| 36–42 days          | 0.94                             | 0.74–1.19 | 0.59  | 0.95                             | 0.81–1.13 | 0.58 | 0.97                             | 0.83–1.14 | 0.71 |
| >42 days            | Reference                        |       |     | Reference                        |       |     | Reference                        |       |     |

\( a \) Adjusted by age, gender, race, comorbidity score, year of diagnosis, patient distance from reporting facility, zip code income, radiation dose, insurance type, and urban/metro/rural residence, and stratified by facility.

### Table 4. Factors associated with radiation initiation >35 days after surgery among patients with gross total resection

| Race                  | Adjusted Odds Ratio | 95% CI | \( P \) |
|-----------------------|---------------------|-------|-----|
| White                 | Reference           |       |     |
| Black                 | 1.41                | 1.05–1.89 | 0.06 |
| Other                 | 1.14                | 0.81–1.59 |     |

| Residence             | Adjusted Odds Ratio | 95% CI | \( P \) |
|-----------------------|---------------------|-------|-----|
| Urban/Rural           | Reference           |       |     |
| Metropolitan          | 1.36                | 1.11–1.66 | 0.003 |

| Distance from reporting facility | Adjusted Odds Ratio | 95% CI | \( P \) |
|---------------------------------|---------------------|-------|-----|
| \( \leq 50 \text{ miles} \)     | Reference           |       |     |
| >50 miles                       | 1.22                | 1.00–1.48 | 0.05 |

| Insurance               | Adjusted Odds Ratio | 95% CI | \( P \) |
|-------------------------|---------------------|-------|-----|
| Medicare                | Reference           |       |     |
| Medicaid/Not insured/Other government | 1.42 | 1.15–1.75 | 0.001 |
| Private/Managed care    | 0.98                | 0.86–1.13 |     |

| Income                  | Adjusted Odds Ratio | 95% CI | \( P \) |
|-------------------------|---------------------|-------|-----|
| \(<\$48\ 000\)         | Reference           |       | 0.03 |
| \(\geq\$48\ 000\) or higher | 0.85 | 0.74–0.98 |     |

Variables with \( P < 0.1 \) were retained in the multivariable logistic model.
postoperative period may induce radioresistance [17], resulting in radiation treatment being less effective. Additionally, as the surgical cavity shrinks over time after surgery, irradiating too early could result in a larger irradiated volume and lead to more toxicity. Finally, selection bias may explain these retrospective findings of survival detriment of early initiation of radiation: patients with the most adverse characteristics are likely the ones who received radiation sooner. For example, Blumenthal found that those receiving radiation earlier were more likely to have a poor performance status, have worse neurologic impairment, have undergone biopsy only, and have a worse recursive partitioning analysis (RPA) class [3].

Thus, we analyzed the time interval between surgery/biopsy and radiation initiation in finer intervals to tease out the various confounders that may be at play. In doing so, we found a trend to inferior survival with early initiation of radiation (within 15 days of surgery) among patients who underwent biopsy only, and believe that this may be due to selection bias as described above. Additionally, patients who received biopsy had worse survival than patients who underwent gross total resection, and they may not have lived long enough to receive the full benefit of early radiation initiation. While it also appeared that among those who had gross total resection, those who initiated radiation within 15 days of surgery did not have improved survival compared with those who had delayed radiation, those patients who initiated radiation within 15 to 35 days of surgery did have a survival benefit. Furthermore, earlier initiation of radiation was associated with improved outcomes, with patients who received radiation within 15–21 days of surgery having the lowest hazard of death compared with those who initiated radiation more than 42 days after surgery. Initiating radiation too early (within 2 weeks of surgery) may not be optimal due to the need for post-operative healing, although there may also be a component of selection bias behind these results.

Interestingly, we found that there are various socio-economic factors that are associated with timely initiation of radiation. Although we cannot deduce the reasons for radiation delay from the NCDB, we found that patients who were black and underinsured, and who lived in metropolitan areas or further away from the treating facility were more likely to have delayed radiation, while patients who lived in higher income zip codes were less likely to receive delayed radiation. We also found similar socio-demographic associations with extent of surgery that patients received. Other have also found similar associations between glioblastoma treatment and outcomes and socio-economic factors such as race and insurance status [18–20].

Limitations of our study include its retrospective nature, lack of correction for multiple testing and lack of important covariates. For example, Karnofsky Performance Status (KPS) and molecular data such as MGMT methylation status were missing for the majority of patients in our cohort. Although we controlled for a large number of observed covariates, there remains the possibility of selection bias and unobserved confounding. However, this is a question that is unlikely to be addressed in the randomized setting. We attempted to address the confounder of performance status by limiting our cohort to those who were robust enough to receive both chemotherapy and radiation within 2 months of surgery. Additionally, NCDB lacks data on tumor progression status. However, because GBM is a highly fatal disease, we expect overall survival to closely mirror progression-free survival.

CONCLUSIONS

In a large cohort of patients with glioblastoma treated with chemotherapy across the country, we found that there may be a survival benefit by initiating radiotherapy within the 35 days following gross total resection. Further work is warranted in understanding barriers to timely access to optimal therapy.

CONFLICT OF INTEREST

Scott G. Soltys is a consultant for Inovio Pharmaceuticals, Inc. There are no conflicts of interest to disclose.

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