Salvage Stereotactic Radiotherapy for Recurrent Glioblastoma Multiforme: Clinical Outcomes from a Multi-Institutional Registry

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Abstract

Objectives: The purpose of this study was to evaluate the potential benefits of dose escalation for overall survival (OS) and assess related toxicities following stereotactic radiotherapy (SRT) for recurrent glioblastoma multiforme (GBM) patients.

Methods: The RSSearch® Patient Registry was screened for patients with recurrent GBM treated with SRT between June 2007 to July 2015. The impact of potential prognostic factors on OS were evaluated using the Kaplan-Meier method and continuous log rank analysis. Prognostic factors examined included prescription dose, GTV, RPA class, initial KPS, patient age, tumor location, and single vs. multifocal recurrence. Logistic regression was utilized to evaluate the relationship between prescription dose and toxicities (graded by CTCAE guidelines).

Results: Forty-seven patients treated with SRT (11 with 3 fractions and 36 with 5 fractions) were identified. Median OS for the cohort was 6.62 months (range: 0.33 months - 38.9 months). Of prognostic factors examined, GTV ≥ 25 cc trended towards poorer prognosis (median OS of 6.23 months vs. 8.63 months; p = 0.0597) as did initial KPS < 70% (2.63 months vs. 8.3 months; p = 0.1168). Patients treated with SRT of 5 fractions and prescription doses ≥ 30 Gy had a higher median OS (8.96 months vs. 5.65 months; p = 0.0904). However, significant survival benefits were not noted from SRT of 5 fractions and prescription doses ≥ 35 Gy (7.61 months vs. 6.47 months; p = 0.4361). Roughly 13% of patients reported side effects such as fatigue, alopecia, and mental status changes with all reported toxicities being either Grade 1 or 2. Doses ≥ 35 Gy for patients treated with SRT of 5 fractions were associated with increased side-effect incidence (p = 0.049).

Conclusion: Salvage SRT was relatively well-tolerated and resulted in similar survival outcomes that have been previously reported in the literature. Dose escalation seems to trend towards better outcomes for SRT of 5 fractions. Prospective studies are warranted to examine the possible benefits of novel adjuvant therapies in combination with SRT given the poor prognosis of recurrent GBM.

Introduction

Glioblastoma multiforme (GBM) is a malignant, high-grade brain tumor that accounts for approximately 2% of adult cancer deaths. GBM has an incidence of roughly 3 to 5 newly diagnosed cases per 100,000 individuals with a preponderance in men, Caucasians, and patients of European descent.1-3 Currently, standard of care for newly diagnosed GBM includes maximal safe resection, conventional radiotherapy (typical dose of 60 Gy), and concurrent temozolomide (75 mg/m2 daily) followed by adjuvant temozolomide. This demonstrated improvements over historical progression-free and overall survival (OS) rates.4 Though median OS has improved (8.1 months to 9.7 months) since temozolomide has been introduced into the treatment of newly diagnosed GBM, prognosis still remains quite poor with reported 5 year survivals ranging from roughly 2-10% and high rates of local recurrence.3,5

Despite these recent developments in the management of newly diagnosed GBM, there is not a consensus on the standard of care for recurrent GBM.6 Similar to newly diagnosed GBM, median OS for recurrent GBM has been historically quite poor at 5 months.5 Repeat surgical resection and second-line mono- or combination chemotherapy with temozolomide or bevacizumab have been attempted to reduce tumor burden and extend OS.5,7,9,10 Though conventional radiotherapy has demonstrated efficacy as a first line therapy for newly diagnosed GBM, it is rarely used to treat recurrent lesions in patients that previously received radiation due to the risk of radionecrosis. However, re-irradiation has been demonstrated to be both safe and provide a survival benefit given advances in radiation technology allowing for more precise targeting of recurrent lesions via stereotactic radiotherapy (SRT).11,12

SRT has been a viable option for accurate delivery of high doses of radiation to intra-cranial targets since first being discussed by Leksell.13 CyberKnife® (Accuray Incorporated, Sunnyvale, CA) is a frameless radiotherapy system based on image-guidance techniques that
provides precise delivery of radiation either in one large dose/over a single fraction (termed stereotactic radiosurgery/SRS) or over multiple fractions (SRT). Utilizing data from a national patient registry, we aimed to examine whether CyberKnife SRT and dose escalation provides a survival benefit for recurrent GBM patients and assess related toxicities stemming from dose escalations. Additionally, we evaluate potential prognostic factors that may be associated with a more favorable survival benefit.

Methods

The RSSearc® Patient Registry began accrual in 2006 and is managed by the Radiosurgery Society®, a non-profit professional medical society. A description of the methodology, database design, and initial patient and treatment characteristics of patients enrolled in RSSearc has been previously reported. All centers treating patients with SRT are offered and encouraged to participate in RSSearc. Participation is voluntary and no compensation is provided either to patients or participating centers. Local Institutional Review Board/Ethics Committee (IRB/EC) approval is required at all participating centers. Informed consent was obtained from all patients, as required by individual IRB/ECs, prior to patient data being entered. As the RSSearc is a multi-institutional registry, treatment planning was performed per institutional guidelines using inverse planning on the MultiPlanSystem® (Accuray Incorporated, Sunnyvale, CA) allowing non-isocentric and non-coplanar radiation delivery using either a ray tracing algorithm or Monte Carlo calculations.

We screened the RSSearc Patient Registry (Clinicaltrials.gov identifier: NCT01885299) for patients with recurrent GBM treated with SRT between June 2007 to July 2015 that had complete data entry fields for screening, treatment, and follow-up (minimum survival data). A total of 47 recurrent GBM patients were identified as having been treated with SRT at various centers participating in RSSearc. Statistical summaries of relevant patient, treatment, and lesion characteristics were performed with descriptive analysis. Possible factors impacting OS were examined via the Kaplan-Meier method and continuous log-rank analysis with p < 0.05 considered statistically significant. Prognostic factors that were evaluated included prescription dose, tumor location, initial Karnofsky Performance Score (KPS), patient age, gross tumor volume (GTV), recursive partitioning analysis (RPA) Class (which incorporates patient age, KPS, and outcomes following surgery to determine prognosis), and whether the recurrence was a single lesion or multifocal. The relationship between side-effect incidence (with toxicities graded based on Common Terminology Criteria for Adverse Events (CTCAE) guidelines) and dose escalation was evaluated via logistic regression or Fisher’s exact test when logistic regression was not possible. All statistical calculations were conducted using Stata 14.0 (StataCorp LP, College Station, TX). Given limited data, local control or progression-free survival was not evaluated.

Results

Patient, lesion, and treatment characteristics

A summary of patient characteristics can be found in Table 1. Median age of recurrent GBM patients was 59 years (range: 8-82). Interestingly, there was a preponderance of female patients (28) as compared to male patients (19) in our cohort despite the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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<tbody>
<tr>
<td>Gender</td>
<td>Female – 28 patients</td>
</tr>
<tr>
<td></td>
<td>Male – 19 patients</td>
</tr>
<tr>
<td>Median Age (range)</td>
<td>59 (8 - 82)</td>
</tr>
<tr>
<td>Median Initial KPS (range)</td>
<td>80% (30% - 100%)</td>
</tr>
<tr>
<td>RPA Class</td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>4 patients</td>
</tr>
<tr>
<td>Class IV</td>
<td>31 patients</td>
</tr>
<tr>
<td>Class V + VI</td>
<td>12 patients</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>40</td>
</tr>
<tr>
<td>African-American</td>
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<tr>
<td>Hispanic</td>
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</tr>
<tr>
<td>Unknown</td>
<td>2</td>
</tr>
<tr>
<td>Prior Treatments Received</td>
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<tr>
<td>Surgical Resection</td>
<td>44</td>
</tr>
<tr>
<td>IMRT</td>
<td>7</td>
</tr>
<tr>
<td>EBRT</td>
<td>41</td>
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<td>SRT</td>
<td>3</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>33</td>
</tr>
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</table>

Table 1: Summary of patient characteristics of recurrent GBM cohort
majority of publications reporting GBM presenting more commonly in males. Eighty percent of patients in the cohort were Caucasian. The vast majority of patients with recurrent GBM had previous surgical resection (88%) for their initial lesion, followed by external beam radiation therapy (EBRT) (82%), chemotherapy (66%), intensity-modulated radiation therapy (IMRT) (14%), and SRT (6%). Given that the standard of care for newly diagnosed GBM includes chemotherapy (temozolomide), surgical resection, and radiotherapy, it is likely that many patients’ initial treatment regimens were subject to under-reporting by participating centers. The median initial KPS prior to treatment was 80% (range: 30% – 100%).

Table 2 provides information regarding characteristics of the lesion as well as radiotherapy planning. Median GTV was 25.445 cc (range: 0.4518 – 265.88 cc), and there was no significant difference in GTV among those receiving 3 fractions (27.065 cc) as opposed to 5 fractions (30.6 cc; p = 0.372). Eighty-eight percent of patients presented with one lesion, 8% with 2 lesions, and 4% with 3 lesions. The most common sites for recurrent GBMs were the temporal lobe (20%), parietal lobe (18%), and frontal lobe (12%). Notably, sixteen percent of recurrent GBM cases were considered surgically inoperable.

In the cohort, 11 patients were treated in 3 fractions and 36 patients were treated in 5 fractions. Median prescription doses for SRT of 3 and 5 fractions were 24 Gy and 30 Gy, respectively. Following treatment, median KPS was unchanged at 80% (range: 40-100%). Roughly 1/3 of the cohort had an increase in KPS following SRT (10% - 30% increase in KPS from baseline), with the other 2/3 of the cohort either experiencing no change or a decline in KPS.

Overall Survival

Median OS based on certain variables of interest as well as relevant probabilities from Kaplan-Meier analysis and log-rank analysis can be found in Table 3. Of prognostic factors evaluated, initial KPS seemed to have the greatest impact on median OS. Although not significantly different (p= 0.1168), patients with an initial KPS of < 70% had median OS of 2.63 months whereas patients with an initial KPS ≥ 70% had a median OS of 8.1 months (Figure 1). Also, patients with GTVs ≥ 25 cc (the cohort median) seemed to have a poorer prognosis with a median OS of 6.23 months as compared to 8.63 months for those with GTVs < 25 cc, though this also was not a significant finding (p = 0.0597; Figure 2).

Other prognostic factors examined, such as RPA Class, age, tumor location, and single vs. multifocal recurrences were found to less correlated with OS. Higher RPA Class seemed to correlate with lower median OS, as Class III, IV and V + VI patients had median OS of 9.52 months, 7.67 months, and 3.38 months, respectively, though was insignificant (p = 0.2695; Figure 3). Median OS for those under the age of 46 was 8.63 months as compared to older patients (6.2 months; p = 0.2655). Recurrent GBM patients with lesions located in frontal, temporal, temporal, parietal, frontal, and occipital lobes were more common. Median OS for recurrent GBMs in the frontal lobe was 9.52 months, in the parietal lobe was 7.67 months, and in the temporal lobe was 6.23 months.

Table 2: Summary of lesion characteristics and radiotherapy planning

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total cohort (25.445 (0.4518 - 265.88))</th>
<th>3 fractions (27.065 (0.4518 - 127.452))</th>
<th>5 fractions (30.6 (4.9 – 265.88))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with surgically inoperable tumors</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median GTV (cc) (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of lesions</td>
<td>1 lesion - 42 patients</td>
<td>2 lesions - 3 patients</td>
<td>3 lesions - 2 patients</td>
</tr>
<tr>
<td>Hemisphere Location</td>
<td>Right – 21 patients</td>
<td>Left – 17 patients</td>
<td>Not specified – 9 patients</td>
</tr>
<tr>
<td>Lesion Location</td>
<td>Temporal Lobe - 10</td>
<td>Parietal Lobe - 9</td>
<td>Frontal Lobe - 6</td>
</tr>
<tr>
<td></td>
<td>Occipital Lobe - 3</td>
<td></td>
<td>Multi-Lobe Involvement - 7</td>
</tr>
<tr>
<td></td>
<td>Other - 3</td>
<td></td>
<td>Not specified -9</td>
</tr>
<tr>
<td>Median Prescribed Dose (Gy) (range)</td>
<td>3 fractions (n = 11): 24 (21 - 30)</td>
<td>5 fractions (n = 36): 30 (10 - 35)</td>
<td></td>
</tr>
<tr>
<td>Median OS (months) (range)</td>
<td>6.62 (0.33 - 38.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median KPS After Treatment (range)</td>
<td>80% (40% - 100%)</td>
<td>Patients with rise in KPS -16 patients</td>
<td>Patients with no change in KPS – 14 patients</td>
</tr>
</tbody>
</table>
pial, or occipital lobes had median survivals of 7.82 months, 8.63 months, 9.57 months, and 14.4 months, respectively (p = 0.317).

The impact of radiation therapy planning on median OS can also be found in Table 3. Patients treated with SRT had a median OS of 6.53 months, and those receiving 3 fractions (5.74 months) did not have significantly different OS than those treated with 5 fractions (6.62 months; p = 0.9011). Median OS was greater in patients who received a prescription dose ≥ 30 Gy (8.96 months) compared to < 30 Gy (5.65 months) for SRT of 5 fractions (p = 0.0904; Figure 4). However, further dose escalation did not seem to result in a survival benefit as patients treated with SRT of 5 fractions and prescription doses ≥ 35 Gy had a median OS of 7.61 as compared to 6.47 months for those treated with < 35 Gy (p = 0.4361; Figure 5). Patients treated with prescription doses ≥ 30 Gy with SRT of 3 fractions had a median OS of 7.05 months compared to those treated with < 30 Gy (4.23 months), though this result was not significant (p = 0.9909).

Toxicities

Incidences of acute and late CNS toxicities following SRT were relatively low. Treatment-related side-effects (Table 4) were documented in roughly 13% of all cases (6/47 patients). The most commonly reported side-effects were fatigue, mental status changes/cognitive dysfunction, alopecia, and speech impairment. Patients reported only CTCAE Grade 1 or 2 toxicities.

Toxicity incidence was not found to be higher for prescription doses ≥ 30 Gy for SRT of 5 fractions (p = 0.193) or prescription doses ≥ 30 Gy for SRT of 3 fractions (p = 0.132). However, dose escalation was found to be related to a higher likelihood of treatment-related toxicities for patients treated with prescription doses ≥ 35 Gy for SRT of 5 fractions (p = 0.049). Also, all patients that had previously been treated with SRT for their initial GBM lesion reported side-effects (p = 0.0112 following Fisher’s exact test). No other previous treatments such as chemotherapy (p = 0.593), IMRT (p = 0.825), EBRT (p = 0.991), or previous surgery (p = 0.773) were associated with a greater likelihood of experiencing treatment-related toxicities.

Discussion

This retrospective study included 47 recurrent GBM patients treated with salvage SRT with a median OS of 6.62 months (range: 0.33 months - 38.9 months). Our results are similar to the findings of Villavicencio, et al., who reported a median OS following SRT for recurrent GBM patients of 7 months (range: 1-34 months) with no correlation found between survival and treatment parameters. Similarly, a retrospective SRT study by Yazici, et al., found similar median GTVs (24 cc; range of 2-81 cc) with a greater median OS (10.6 months; range: 1.1 - 20 months).

Notably, we were unable to comment on the benefits of SRS in our study due to lack of an adequate sample size (n = 3). The results of Patel, et al., suggest that SRS (median OS: 8.5 months) may provide a survival advantage over SRT (median OS: 7.4 months), though this was not a significant finding. Cho, et al., reported similar OS between SRS (median OS: 11 months) and SRT (median OS: 12 months), though patients receiving SRT had poorer prognostic factors than those of the SRS group. Studies reporting on GammaKnife® SRS for recurrent GBM have documented median OS to range anywhere from 9 to 17.9 months.

With regards to prognostic factors, one of the largest SRT retrospective series published to date completed by Fogh, et al., found that younger age (p = 0.001) and lower GTV (p = 0.025) were associated with higher OS following SRT for recurrent high-grade gliomas. Our study did not find age to be significantly correlated with median OS, likely due to our smaller cohort (47 patients vs. 147 patients), though...
GTVs $< 25$ cc trended towards better outcomes (median OS of 8.63 months vs. 6.23 months; $p = 0.0597$). Similarly, Yazici, et al., have reported that patients with GTV $< 24$ cc have significantly better outcomes following SRT ($p = 0.015$). Though RPA Class has been established as a significant prognostic factor for newly diagnosed GBM and higher RPA Class trended towards poorer outcomes in our cohort, this also was not significant ($p = 0.2695$).

In prior studies examining SRT for recurrent GBM, no major toxicities were noted following treatment similar to our results. Higher doses SRT plans (6 fractions of 7 Gy) have also been utilized without severe toxicities noted. With regards to single fraction SRS, studies have found that 33% of recurrent glioma patients with GTVs $> 20$ cc treated with SRS required operation due to increased intracranial pressure secondary to radio-necrosis. Others have reported that anywhere from 10-38% of SRS treated patients reported CNS radio-induced necrosis, with other serious side-effects including hemiparesis, vision loss, severe edema, and vascular injuries such as carotid artery stenosis.

With regards to dose escalation, Fogh, et al., have reported that higher prescription doses trended towards better survival outcomes for high-grade glioma patients as prescription doses $\geq 35$ Gy nearly reached significance ($p = 0.07$). In our cohort, prescription doses $\geq 35$ Gy for SRT of 5 fractions did not seem to result in a significant survival benefit (median OS of 7.61 months as compared to 6.47 months; $p = 0.4361$), though this is likely due to the small number of patients (4) receiving $\geq 35$ Gy. Other studies have demonstrated higher median OS following prescription doses of $\geq 30$ Gy (11.1 months) as opposed to $< 30$ Gy (7.4 months), which was also close to reaching statistical significance ($p = 0.0904$). These findings are quite similar to those of our study, as patients receiving doses $\geq 30$ Gy in 5 fractions were found to have a higher median survival (8.96 months) than those receiving $< 30$ Gy (5.65 months; $p = 0.0904$).

Of note are the findings of Conti, et al., who demonstrated a substantial survival advantage for recurrent GBM patients treated with SRT and an intensive regimen of temozolomide (median OS: 12 months) as compared to SRT alone (median OS: 7 months) ($p < 0.01$). However, following this regimen, the incidence of major adverse effects was >40%. Other studies examining the concurrent use of salvage SRT with other treatment modalities are warranted given that concurrent chemotherapy (i.e. temozolomide and bevacizumab)

| Table 3: Evaluation of Potential Prognostic Factors and Radiotherapy Planning on Median OS |
|---------------------------------------------|-----------------|-----------------|-----------------|
| **Variable**                              | **Number of Patients** | **Median OS**   | **p-value**     |
| RPA Class                                 |                  |                 | 0.2695          |
| Class III                                 | 4                | 9.52 months     |                 |
| Class IV                                  | 31               | 7.67 months     |                 |
| Class V + VI                              | 12               | 3.38 months     |                 |
| Initial KPS                               |                  |                 | 0.1168          |
| $< 70\%$                                  | 7                | 2.63 months     |                 |
| $\geq 70\%$                               | 40               | 8.1 months      |                 |
| Tumor Location                            |                  |                 | 0.317           |
| Frontal                                   | 6                | 7.82 months     |                 |
| Temporal                                  | 10               | 8.63 months     |                 |
| Parietal                                   | 9                | 9.57 months     |                 |
| Occipital                                 | 3                | 14.4 months     |                 |
| Age                                       |                  |                 | 0.2655          |
| $< 46$ years                               | 6                | 8.63 months     |                 |
| $\geq 46$ years                           | 41               | 6.2 months      |                 |
| GTV                                        |                  |                 | 0.0597          |
| $< 25$ cc                                 | 23               | 8.63 months     |                 |
| $\geq 25$ cc                              | 24               | 6.23 months     |                 |
| Single or Multifocal Recurrence            |                  |                 | 0.5591          |
| 1 lesion                                  | 42               | 7.7 months      |                 |
| $> 1$ lesion                              | 5                | 6.33 months     |                 |
| Prescription Dose (5 fractions)            |                  |                 | 0.9909          |
| $< 30$ Gy                                 | 15               | 5.65 months     | 0.0904          |
| $\geq 30$ Gy                              | 19               | 8.96 months     |                 |
| $< 35$ Gy                                 | 32               | 6.47 months     | 0.4361          |
| $\geq 35$ Gy                              | 4                | 7.62 months     |                 |
| Prescription Dose (3 fractions)            |                  |                 | 0.9909          |
| $< 30$ Gy                                 | 7                | 4.23 months     |                 |
| $\geq 30$ Gy                              | 4                | 7.05 months     |                 |
with SRT have proven to be relatively safe. Studies examining combinations of salvage SRS followed by bevacizumab demonstrated significantly improved median OS (18 months) as compared to those who received salvage SRS alone (12 months; p = 0.005) as well as a lower risk of adverse side-effects (9% as opposed to 46%, p = 0.037).

One major limitation of our study is the inability to comment on either progression free survival or local control given insufficient data on these parameters. Additionally, the small sample size of the cohort limits the power and thus generalizability of our findings and observations. Notably, RPA Class, initial KPS, GTV, and prescription doses ≥ 30 Gy for SRT of 5 fractions correlated with median OS but were statistically insignificant. Finally, our analysis lacks information regarding other data of interest that have likely have prognostic implications meriting study, such as the initial radiation dose received, the length of the disease free interval (DFI), the time interval between initial conventional radiotherapy and retreatment with SRT, and the extent of surgical resection.

Conclusion
This study contributes to the growing body of knowledge regarding the efficacy of SRT for the treatment of recurrent GBM. Radiation therapy was well-tolerated with most patients experiencing minor toxicities that resolved shortly following treatment. Dose escalation appears to trend towards improved median OS as is consistent with other studies. Prospective studies are warranted given the continuing poor prognosis for recurrent GBM with the goal of identifying novel concurrent or adjuvant therapies that improve OS without incurring serious adverse toxicities.

References

Figure 2. Kaplan-Meier Analysis Examining Impact of GTV on Recurrent GBM Median OS

Figure 3. Kaplan-Meier Analysis Examining Impact of RPA Class on Recurrent GBM Median OS
Figure 4. Kaplan-Meier Analysis Examining Benefit of Doses ≥ 30 Gy for SRT of 5 fractions

Figure 5. Kaplan-Meier Analysis Examining Benefit of Doses ≥ 35 Gy for SRT of 5 fractions


**Table 4 – Summary of Patient-Reported Toxicities following SRT**

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<thead>
<tr>
<th>CTCAE Grade 1 Toxicities (4/47 patients)</th>
<th>CTCAE Grade 2 Toxicities (2/47 patients)</th>
</tr>
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<tbody>
<tr>
<td>Fatigue – 3</td>
<td>Alopecia - 2</td>
</tr>
<tr>
<td>Mental Status Change/Cognitive Dysfunction – 2</td>
<td>Mental Status Change/Cognitive Dysfunction – 1</td>
</tr>
<tr>
<td>Speech Impairment – 1</td>
<td>Speech Impairment – 1</td>
</tr>
<tr>
<td>Generalized Pain – 1</td>
<td>Blurred Vision – 1</td>
</tr>
<tr>
<td>Insomnia – 1</td>
<td>Head and Neck Edema – 1</td>
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