Glioblastoma multiforme is the most common and aggressive primary malignant brain tumor in adults. Despite recent advances in neuroimaging, surgical techniques, and adjuvant therapies such as chemotherapy and EBRT, GBM has a dismal prognosis, with local recurrence remaining the most common form of relapse in more than 80% of patients. Surgical treatment of a focal recurrence can lead to prolonged growth control, but this procedure is only offered to a small subpopulation. Systemic chemotherapy provides a modest survival advantage, with the median survival ranging from 4 to 7 months in patients with recurrent disease.

Stereotactic radiosurgery, fSRT, and brachytherapy are logical adjuncts to current state-of-the-art treatments for recurrent GBM because of their ability to deliver high doses of radiation to a focal target. In addition, state-of-the-art neuroimaging techniques, such as MR spectroscopic imaging, diffusion tensor tractography, and nuclear medicine imaging, have enhanced treatment planning methods leading to potentially improved clinical outcomes. In this paper the authors reviewed the current applications and efficacy of SRS and fSRT in the treatment of GBM, highlighting the value of these therapies for recurrent focal disease. 

**Key Words** • stereotactic radiosurgery • image guidance • fractionated stereotactic radiotherapy • robotics • glioblastoma multiforme • recurrent disease

**Abbreviations used in this paper:** BCNU = bischloroethylnitrosourea; EBRT = external beam radiotherapy; fSRT = fractionated stereotactic radiotherapy; GBM = glioblastoma multiforme; KPS = Karnofsky Performance Scale; LINAC = linear accelerator; RPA = recursive partitioning analysis; RTOG = Radiation Therapy Oncology Group; SRS = stereotactic radiosurgery; TMZ = temozolomide.

Stereotactic radiosurgery, fSRT, and brachytherapy are logical adjuncts to current state-of-the-art treatments for recurrent GBM because of their ability to deliver high doses of radiation to a focal target. In comparing these options, radiosurgery appears to be the most convenient, offering a fast, noninvasive treatment that can be completed in one day, is usually well tolerated, and can be repeated.

The main limitation of focal treatments is their inability to address diffuse disease, which in many cases has already developed microscopic lesions far beyond the limits of appreciable radiological boundaries. Nonetheless, developments in medical imaging have enabled the neurosurgeon to accurately visualize functional and biomolecular data from both the normal and diseased brain. New modalities of information may complement simple anatomical representations of the brain to facilitate safer and more efficient therapeutic approaches to brain tumors. In particular, the inclusion of PET and MR spectroscopic, fMR, and diffusion tensor imaging.
in treatment planning can enhance the coverage of diseased brain areas by showing the diffusion of gliomas along pathways following the subcortical fiber tracts, the presence of distant regions of hypermetabolism, and the involvement of critical areas. This information can help define a planning target volume that is not simply a geometrical expansion of the gross tumor volume.

On these bases, the ability to deliver focal high-dose radiation, ablating a selected volume while preserving normal tissue, has a valuable role in the global treatment of recurrent disease. A number of early retrospective studies on the use of SRS and fSRT for recurrent GBM have shown promise.\(^{29,31,42,54}\) In this paper, we discuss the role of SRS and fSRT in the multimodal treatment of this disease, with particular emphasis on the treatment of focal relapse.

**Supplementing Radiation Doses to Recurrent High-Grade Gliomas**

Treatment modalities delivering highly focused radiation can be used to boost the dose delivered to a GBM via conventional irradiation techniques while minimizing radiation exposure to adjacent areas of brain. The goal of local GBM treatments is to increase the duration of survival while maintaining an acceptable quality of life for the patient. The various methods of adding radiation doses are SRS, fSRT, and brachytherapy (with or without hyperthermia) with the implantation of seeds or a novel brachytherapy device called the GliaSite Radiation Therapy System (Cytc Corp.). Two large Phase III trials have been focused on brachytherapy;\(^{56,62}\) standard EBRT alone was compared with EBRT plus low-activity \(^{125}\)I seed implants, but no significant survival advantage was demonstrated by the addition of brachytherapy. Smaller Phase II studies have yielded various results.\(^{29,31,42,54,68}\) The addition of hyperthermia to brachytherapy has demonstrated a statistically significant survival advantage in 2 small patient cohorts.\(^{70,72}\) Despite these favorable results, no large-scale randomized study has been performed to confirm these findings. The implantation of permanent \(^{125}\)I seeds has also been described recently. Permanent low-activity seeds seem to be associated with lower rates of radiation necrosis\(^{29,31,42,54}\) compared with the rates resulting from the implantation of temporary high-activity seeds.\(^{3,69,85}\)

A new approach to brachytherapy is the GliaSite Radiation Therapy System, a balloon catheter system implanted in the surgical cavity that includes a reservoir to hold an aqueous solution of organically bound \(^{125}\)I (sodium 3-[\(^{125}\)I]-iodo-4-hydroxybenzenesulfonate, or Iotrex) to deliver low-dose radiation through a subcutaneous port.\(^{79}\) The efficacy of GliaSite brachytherapy was assessed in 24 patients with recurrent GBM.\(^{11}\) The median survival duration following GliaSite treatment was 9.1 months and was comparable to historical data. Patients with a KPS score of at least 70 survived longer than those with a score < 70 (9.3 months compared with 3.1 months, respectively; \(p = 0.003\)). Although this approach has been shown to be feasible and safe in patients with recurrent malignant glioma, it is not in widespread use because of the absence of large-scale, randomized clinical data; the inconvenience to the patient, who must be isolated during treatment; and the necessity of a second surgery to remove the delivery system once treatment is completed. Furthermore, the application of GliaSite is limited to patients with small, superficial lesions that are amenable to resection.

While the main limitation of brachytherapy is its invasiveness, SRS and fSRT are virtually noninvasive, especially when frameless technologies are used.\(^{29,66}\) Although various terms exist in the literature, the term “SRS” typically refers to single-fraction stereotactic radiation treatment, whereas the term “fSRT” is used when several stereotactic radiation fractions are delivered. Hypofractionated radiosurgery is an emerging technique for delivering highly precise and accurate irradiation, dividing the total dose in up to 5 fractions.\(^{7}\) Devices suitable for SRS and fSRT treatment include LINAC-based systems that use x-ray beams generated from a linear accelerator and a stereotactic frame for target localization. The Gamma Knife (Elekta) utilizes 201 individual \(^{60}\)Co gamma-ray sources placed within a helmet-like configuration. A stereotactic frame is required to immobilize the head and precisely direct the cross-fired beams to the target. The CyberKnife (Accuray, Inc.) is a robotic, LINAC-based radiosurgery device that obviates the need to apply an invasive frame to the patient’s skull. The Novalis LINAC-based device (BrainLAB) offers frame-based treatment for SRS and frameless treatment for fSRT.

Initial enthusiasm for SRS as an adjunct in glioma management was dampened after the publication of data from a large Phase III study conducted by Southam and coworkers\(^{71}\) on behalf of the RTOG. In this study, 203 patients with newly diagnosed malignant gliomas were randomized to receive EBRT plus BCNU\(^{7}\) or SRS plus EBRT plus BCNU. Data in this study failed to demonstrate a survival advantage in the patients who received the additional SRS boost as part of the initial management strategy. The SRS group had a median survival time of 13.5 months, whereas the control group had a median survival of 13.6 months. While the authors concluded that SRS before EBRT and BCNU did not improve survival for newly diagnosed GBM, they did not address the delivery of SRS alone as a boost or the use of SRS in the treatment of recurrent disease.

**Stereotactic Radiosurgery and fSRT for the Treatment of Recurrent GBM**

Authors of several retrospective studies (Table 1) have reported that SRS is associated with prolonged survival in patients with recurrent GBM. These studies have shown median survival times ranging from 7.5 to 30 months.\(^{23,30,33,36,40,47}\) A recent case-control study has indicated that patients with recurrent GBM treated with SRS require fewer surgical procedures and experience a slightly longer survival as compared with untreated patients.\(^{57}\) This and other retrospective studies have suggested a life-prolonging effect of SRS in the management of recurrent GBM.\(^{35,40,47,97}\)

Kondziolka et al.\(^{36}\) have evaluated the survival benefit of SRS in 64 patients with GBM compared with historical
Role of stereotactic radiosurgery for recurrent GBMs

TABLE 1: Summary of published studies on radiosurgery treatments for recurrent GBMs*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Recurrent GBMs/No. of Gliomas</th>
<th>No. of Fractions</th>
<th>Total Median Dose in Gy (range)</th>
<th>Median Tumor Size in ml (range)</th>
<th>Reop Rate (%)</th>
<th>Median Survival From Reirradiation (mos)</th>
<th>Actuarial Overall Survival (%) 1 Year 2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hall et al., 1995</td>
<td>26/35</td>
<td>1</td>
<td>20 (12–25)</td>
<td>6.5 (0.88–31.2)</td>
<td>19‡</td>
<td>7.5</td>
<td>74 NA 36 NA</td>
</tr>
<tr>
<td>Shrieve et al., 1999</td>
<td>86/118</td>
<td>1</td>
<td>13 (6–20)</td>
<td>10.1 (2.2–83)</td>
<td>22§</td>
<td>10.2</td>
<td>45 NA 19 NA</td>
</tr>
<tr>
<td>Larson et al., 1996</td>
<td>66/189</td>
<td>1</td>
<td>16 (9–30)</td>
<td>6.5</td>
<td>—</td>
<td>14.25‡</td>
<td>56 NA 34 NA</td>
</tr>
<tr>
<td>Kondziolka et al., 1997</td>
<td>64**/107</td>
<td>1</td>
<td>15.5 (12–25)</td>
<td>6.5 (0.88–31.2)</td>
<td>19†</td>
<td>30</td>
<td>NA 51 NA</td>
</tr>
<tr>
<td>Combs et al., 2005**</td>
<td>32/NA</td>
<td>1</td>
<td>15 (10–20)</td>
<td>10 (1–54)</td>
<td>18 (10‡)</td>
<td>42‡‡</td>
<td>90 NA 49 NA</td>
</tr>
<tr>
<td>Mahajan et al., 2005</td>
<td>41/61</td>
<td>1</td>
<td>18 (12–20)</td>
<td>10.4 (0.3–60.1)</td>
<td>11 (7.6‡; 3.8‡)</td>
<td>8.4</td>
<td>NA NA</td>
</tr>
<tr>
<td>Hejne et al., 2005 **</td>
<td>26/51</td>
<td>1</td>
<td>24 (15–32)</td>
<td>13.6 (0.6–64.4)</td>
<td>57†‡ (31§)</td>
<td>10</td>
<td>68†‡ 30†‡ NA</td>
</tr>
<tr>
<td>Cho et al., 1999</td>
<td>15/71</td>
<td>1</td>
<td>17</td>
<td>10 (1–54)</td>
<td>18 (10‡)</td>
<td>11</td>
<td>42‡‡ 11‡‡</td>
</tr>
<tr>
<td>Larson et al., 1996</td>
<td>10/NA</td>
<td>6</td>
<td>36 (18–36)</td>
<td>15.7 (3.1–29.0)</td>
<td>28 (21§)</td>
<td>14.2</td>
<td>50 NA</td>
</tr>
<tr>
<td>Hudes et al., 1999</td>
<td>19/20</td>
<td>8–10</td>
<td>(25–35)</td>
<td>12.66 (0.89–47.5)</td>
<td>26†</td>
<td>10.5</td>
<td>20 NA</td>
</tr>
<tr>
<td>Vordermark et al., 2005</td>
<td>14/19</td>
<td>4–6</td>
<td>30 (20–30)</td>
<td>15 (4–70)</td>
<td>—</td>
<td>9.3</td>
<td>26 16</td>
</tr>
<tr>
<td>Combs et al., 2005**</td>
<td>59/172</td>
<td>5</td>
<td>36 (12–20)</td>
<td>10.4 (0.3–60.1)</td>
<td>11 (7.6‡; 3.8‡)</td>
<td>8.4</td>
<td>NA NA</td>
</tr>
<tr>
<td>Lederman et al., 1997</td>
<td>14/NA</td>
<td>4 + CT</td>
<td>24 (18–36)</td>
<td>15.7 (3.1–29.0)</td>
<td>28 (21§)</td>
<td>14.2</td>
<td>50 NA</td>
</tr>
<tr>
<td>Lederman et al., 2000</td>
<td>88/NA</td>
<td>4 + CT</td>
<td>24</td>
<td>12.7 (1.5–50.3)</td>
<td>12 (8‡; 2‡)</td>
<td>7</td>
<td>40 NA</td>
</tr>
<tr>
<td>Wurm et al., 2006</td>
<td>18/25</td>
<td>5–6 + CT</td>
<td>25–30</td>
<td>16.1 (1.5–29.3)</td>
<td>—</td>
<td>5.7</td>
<td>8 NA NA</td>
</tr>
<tr>
<td>Schwer et al., 2008</td>
<td>11/15</td>
<td>3 + CT</td>
<td>18–36</td>
<td>41 (12–151)</td>
<td>18‡</td>
<td>10</td>
<td>40 NA</td>
</tr>
<tr>
<td>Pouratian et al., 2009</td>
<td>26/48</td>
<td>1</td>
<td>6 (3–15)</td>
<td>21.3 (0.3–110.0)</td>
<td>4.2**††</td>
<td>9.4</td>
<td>NA NA</td>
</tr>
</tbody>
</table>

* In studies examining more than 1 target type, results are presented for recurrent GBM only unless otherwise noted. Abbreviations: CT = chemotherapy; NA = not available.
† Reoperation for progression.
‡ Reoperation for necrosis.
§ Reason for reoperation unknown.
¶ If treatment criteria not met, 10 months.
** Includes nonrecurrent.
†† In total series.
‡‡ Statistically insignificant differences between fSRT and SRS.

controls. In contrast to those in the study by Souhami and colleagues,71 patients received adjuvant SRS 5–8 months after the initial diagnosis (and after other therapies had been completed, including EBRT and chemotherapy) either before or at the time of disease progression. The median survival time after the initial diagnosis was 26 months, the median survival time after radiosurgery was 21 months, and the 2-year survival rate was 51%. Kondziolka and colleagues36 have also reported a median survival of 30 months after treatment in patients who underwent SRS at the time of tumor progression.

Linear accelerator–based radiosurgery has also been used in the treatment of high-grade gliomas.66,67 Shrieve et al.67 have reported data on 86 patients who had undergone LINAC SRS at the time of tumor recurrence (median radiation dose 13 Gy, median tumor volume 10.1 cm³). The median duration of actuarial survival was 10.2 months. The 12- and 24-month survival rates were 45 and 19%, respectively. These authors identified 2 prognostic factors: age and tumor volume. Patients younger than the median age of 46 years had a median actuarial survival of 15.5 months, compared with 8.2 months for older patients (p = 0.005). Those with tumor volumes smaller than 10.1 cm³ also survived longer after SRS than the patients with larger tumors; median survivals were 15.1 and 8.1 months, respectively (p = 0.007). Both a young age and a small tumor volume remained positive prognostic factors on multivariate analysis (relative risk 0.829 and 0.707, respectively; p < 0.005). According to those data the addition of a radiosurgery boost appears to confer a survival advantage.

A number of retrospective studies have been published on the treatment of recurrent GBM using fSRT regimens (Table 1). Combs et al.21 have published a retrospective study on 59 patients with recurrent GBM. The median survival following fSRT was 8 months, with an
overall median survival of 21 months from the time of initial diagnosis. These authors concluded that fSRT was a safe and well-tolerated strategy warranting further evaluation. Vordermark et al. have performed a retrospective study of 14 patients with recurring GBMs that were treated with 4–6 fractions of 5 Gy of radiation. Overall survival in those receiving a total dose of 30 Gy of radiation was 11.1 months, as compared with 7.4 months in those receiving < 30 Gy. The median survival for all patients was 9.3 months from the time of fSRT. These authors also found that the combination of fSRT with other salvage treatments was associated with longer-term survival, whereas the median survival from the time of treatment was comparable to that with SRS treatments.

The CyberKnife is a frameless radiosurgical device that can be used to deliver SRS or fSRT in regimens depending on physician criteria, primarily in consideration of the tumor volume (Fig. 1). A multicenter study involving treatment facilities spread across the US and Europe has confirmed a potential role for CyberKnife radiosurgery in the treatment of malignant gliomas. The study was aimed at establishing local tumor control of newly diagnosed versus recurrent GBMs as well as determining if this treatment modality could improve survival rates. Forty-six patients were treated at multiple institutions between August 2002 and September 2005. Twenty patients (43.5%) underwent CyberKnife treatment at the time of initial diagnosis and/or during the first 3 months of their initial clinical treatment. Twenty-six patients (56.5%) were treated at the time of tumor recurrence or progression. The median survival (Kaplan-Meier analysis) among patients treated with the CyberKnife as an initial clinical therapy was 11.5 months, as compared with 24 months among those treated at the time of tumor recurrence or progression; this difference was statistically significant (p < 0.0004). A Cox proportional hazards survival re-
Regression analysis demonstrated that survival time had no statistically significant correlations with CyberKnife treatment parameters (maximum dose [Dmax], minimum dose [Dmin], and number of fractions) or target volume. Survival time and RPA class was not quite statistically significant between patients who received CyberKnife treatment as an initial clinical therapy and those treated at the time of tumor recurrence or progression (p = 0.07). The extent of the surgical intervention significantly affected survival time (p = 0.008), especially if a biopsy procedure as opposed to total tumor resection was performed (p = 0.004). There were no statistically significant differences in these parameters between newly diagnosed and recurrent GBM groups (t-test).

A few studies have also focused on SRS and fSRT in combination with chemotherapy for recurrent GBMs (Table 1). One prospective study of SRS in conjunction with marimastat for recurrent gliomas showed no survival advantage for patients with recurrent GBM. Other trials have shown that the multimodality treatment of stereotactic radiosurgery, radiotherapy, and chemotherapy is feasible and well tolerated, with survival times similar to those for other treatment modalities.

Criteria for the Selection of Candidate Patients

One limitation of the retreatment of recurrent malignant glioma is the high risk of radiation-induced complications. It has been shown that for gliomas, the higher the dose the longer the patients survive—but along with a higher dose comes a higher rate of complications. Such complications include radiation necrosis, cranial nerve neuropathies, vascular injuries (including carotid artery stenosis), and severe edema. A study by the RTOG evaluated the toxicity of the radiosurgical treatment of previously irradiated malignant gliomas, escalating the dose to 24 Gy. They demonstrated a good tolerance for small and medium-sized tumors but unacceptable toxicity for larger lesions. Combs et al. have treated 32 patients with recurrent gliomas using SRS; a median dose of 15 Gy was applied to a median target volume of 10 ml. During follow-up, no severe treatment-related side effects were observed, and the median survival from SRS treatment was 10 months. Note, however, that other groups have reported higher incidences of treatment-related side effects, especially with larger target volumes. In a study published by Hall et al., 14% of the patients had radiation-induced necrosis, and survival calculated from the SRS treatment was 8 months. The comparably high rate of severe side effects might be attributable to the relatively larger lesion volumes (median 28 cm³) treated with SRS. The higher rate of necrosis might also be due to the applied higher median dose of 20 Gy.

One issue the SRS studies raise is the number of reoperations required because of radiation necrosis. Several of the SRS studies have documented high necrosis-related reoperation rates ranging from 10 to 31%. Hsieh et al. have suggested that their necrosis-related reoperation rate of 31% may be attributable to large tumor sizes, but the cause of radiation necrosis in these cases remains unclear. Other authors have suggested that fSRT treatments have a radiobiological advantage that can reduce radiation-induced necrosis. Consequently, dose-escalation studies and fSRT treatment regimens for recurrent GBM were examined. Cho et al. have performed a retrospective analysis of recurrent GBM treatment by comparing SRS with fSRT. These authors found that patients treated using fSRT had survival times comparable with those in patients treated using SRS even though the prognostic...
factors of the fSRT patients were worse before treatment. Hudes et al. have performed a Phase 1 dose-escalation study in 19 patients with persistent or recurrent GBM. No Grade 3 toxicities or need for reoperation were reported in this study. The median survival time from the completion of fSRT was 10.5 months, with a 20% 1-year survival rate. These authors concluded that their encouraging response of fSRT was 10.5 months, with a 20% 1-year survival rate. Patel et al. have reported findings on 36 patients with recurrent GBM. At the time of recurrence, 26 patients were treated using SRS with a median dose of 18 Gy to a median tumor volume of 10.4 ml. Ten patients were treated with fSRT using a radiation dose of 36 Gy in 6 fractions to a median lesion volume of 51.1 ml. The median survival time after SRS was 8.5 months, compared with 7.4 months after fSRT (p = 0.81). The reoperation rate was not statistically different between the SRS and fSRT groups. This finding could suggest that the adequate selection of radiation doses and fractionation in relation to lesion volume can lead to a good response and low complication rates.

The volume of tumor and relative volume of irradiated normal brain are therefore critical factors. Reirradiation of normal perilesional brain tissue can easily result in exceeding the cumulative normalized total dose of > 100 Gy that is considered critical for the development of radionecrosis in the brain. Dose/volume calculations can be obtained according to the linear quadratic model, using an α/β = 10 for the tumor and an α/β = 2 for normal brain (Fig. 2). In Table 2 some dose and fractionation examples are listed. The volume of normal brain included in the isodoses can be calculated by obtaining the corresponding cumulative normalized total dose to provide an estimate of the risk of radionecrosis.

Other reported selection criteria for treatment include a KPS score of at least 50–60, a life expectancy > 3 months, a younger age, and a histopathological diagnosis of GBM. Larson et al. have analyzed selection factors for a variety of primary and recurrent WHO Grade II–IV gliomas. They found that the favorable criteria for SRS included unifocal tumors; tumors located in hemispheric, supratentorial subcortical sites; a patient age younger than 70 years; and a KPS score > 60. Shrieve et al. have found that increased survival times were associated with SRS (p = 0.81). The reoperation rate was not statistically different between the SRS and fSRT groups. This finding could suggest that the adequate selection of radiation doses and fractionation in relation to lesion volume can lead to a good response and low complication rates.

The combination of new technologies for highly conformal radiation delivery and advanced neuroimaging methods may offer the opportunity for improved results in the treatment of high-grade gliomas. The most likely reason why radiotherapy is not very effective in long-term disease control lies in the failure to identify the spreading pattern of gliomas. With current radiation treatment modalities, the volume to be irradiated typically incorporates a 20-mm isotropic margin to account for microscopic tumor spread; however, distant or progressive tumors occur outside this margin. Furthermore, both target definition and tumor grading with conventional MR imaging data to plan radiotherapy treatment have limitations. The Gd-enhancing lesion, as seen on T1-weighted MR imaging, reflects regions where there has been a breakdown of the blood–brain barrier. The enhancing lesions may not be a reliable indicator of active tumor because of the concomitant presence of nonenhancing actively growing tumor tissue. Similarly, a T2-defined volume either overestimates or underestimates the microscopic or nonenhancing disease in a majority of patients.

**Future Perspectives**

Advancements in defining the target volume—as provided by state-of-the-art neuroimaging such as MR spectroscopic imaging, diffusion tensor tractography, and nuclear medicine imaging methods (Fig. 3)—offer new chances to improve the evaluation of gross tumor volume and clinical target volume. Advanced neuroimaging techniques and metabolic imaging may disclose brain areas in which tumor diffusion is already present, notwithstanding the absence of contrast enhancement on conventional anatomical imaging. In particular, MR spectroscopy and PET can provide information on the altered metabolic activity of tumor cells and functionally critical brain tissues, and so guiding the dose painting in the treatment planning for

<table>
<thead>
<tr>
<th>Radiation Dose</th>
<th>Glioma (Gy)</th>
<th>Normal Brain (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NTD10, Isodose 80%</td>
<td>NTD10, Isodose 100%</td>
</tr>
<tr>
<td>18 Gy</td>
<td>61</td>
<td>71</td>
</tr>
<tr>
<td>20 Gy in 2 fractions</td>
<td>56</td>
<td>64</td>
</tr>
<tr>
<td>18 Gy in 3 fractions</td>
<td>50</td>
<td>56</td>
</tr>
<tr>
<td>24 Gy in 3 fractions</td>
<td>57</td>
<td>66</td>
</tr>
<tr>
<td>25 Gy in 5 fractions</td>
<td>55</td>
<td>61</td>
</tr>
</tbody>
</table>

* NTD = normalized total dose.
Role of stereotactic radiosurgery for recurrent GBMs

### TABLE 3: Factors that may affect the outcomes of SRS or fSRT for recurrent GBM

<table>
<thead>
<tr>
<th>Potential Prognostic Factor</th>
<th>Description</th>
<th>Authors &amp; Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>prescribed dose</td>
<td>response correlated to total dose (p = 0.0056) in a 3 Gy/fraction fSRT treatment; none of lesions treated w/ 21 or 24 Gy responded, whereas there was a 79% response rate among lesions treated w/ 30 or 35 Gy</td>
<td>Hudes et al., 1999</td>
</tr>
<tr>
<td>tumor vol</td>
<td>survival was longer after a total dose of 30 Gy delivered in 5–6 fractions (11.1 mos) than after total doses of &lt;30 Gy delivered in 2–5 fractions (7.4 mos; p = 0.051) patients w/ tumor vols smaller than 10.1 cm$^3$ survived longer after SRS than patients w/ larger tumors; median survivals were 15.1 and 8.1 mos, respectively (p = 0.007) tumor vols ≤20 ml associated w/ higher likelihood of response (p = 0.053) after fSRT</td>
<td>Vordermark et al., 2005 Shrieve et al., 1999 Hudes et al., 1999</td>
</tr>
<tr>
<td>age</td>
<td>patients younger than the median age of 46 years had a median actuarial survival of 15.5 mos, compared w/ 8.2 mos for older patients (p = 0.005) younger age (p = 0.0405) associated w/ improved survival on multivariate analysis</td>
<td>Shrieve et al., 1999 Hall et al., 1995</td>
</tr>
<tr>
<td>KPS score</td>
<td>KPS score &gt;90 associated w/ prolonged survival on multivariate analysis</td>
<td>Hsieh et al., 2005</td>
</tr>
<tr>
<td>RPA class</td>
<td>RPA Class 3 patients had better outcome as compared with historical series RPA Class 3 patients had median survival time of 29.5 mos after diagnosis; significantly longer than the median survival times for Classes 4 and 5, which were 19.2 and 18.2 mos, respectively (p = 0.001)</td>
<td>Pouratian et al., 2009 Shrieve et al., 1999</td>
</tr>
<tr>
<td>morphology</td>
<td>unifocal tumors, tumors located in hemispheric, supratentorial subcortical sites had better outcome</td>
<td>Larson et al., 1996</td>
</tr>
<tr>
<td>corticosteroid dependency</td>
<td>survival inversely correlated w/ corticosteroid treatment dependency at the time of SRS</td>
<td>Pouratian et al., 2009</td>
</tr>
<tr>
<td>fractionation</td>
<td>fSRT may be a better option for patients w/ larger tumors or lesions in eloquent structures</td>
<td>Cho et al., 1999</td>
</tr>
<tr>
<td>concurrent chemotherapy</td>
<td>adjuvant chemotherapy was associated w/ increased survival on multivariate analysis</td>
<td>Hsieh et al., 2005</td>
</tr>
<tr>
<td>extent of resection</td>
<td>extent of surgical intervention (gross-total vs biopsy) significantly affected survival time (p = 0.008)</td>
<td>Villavicencio et al., 2009</td>
</tr>
<tr>
<td>response to radiation</td>
<td>survival significantly improved among patients who either responded or had stable disease after salvage reirradiation as compared with nonresponders</td>
<td>Patel et al., 2009</td>
</tr>
</tbody>
</table>

Diffusion tensor imaging, a technique that displays the distribution and abnormalities of white matter fibers resulting from tumor infiltration, has also been included in the treatment planning for gliomas. In one study elongated treatment margins along the paths of increased water diffusion and altered metabolic activity were included in the treatment volume, to some extent creating a model of tumor diffusion. Including a diffusion prediction model generates a further radiobiological parameter that is the image-based high-risk volume. Future fSRT and SRS treatment volumes could be modified according to the biological tumor volume and image-based high-risk volume, and thus create a biologically better treatment plan that may reduce the incidence of progression. Another opportunity to improve the efficacy of SRS and fSRT in the management of recurrent GBMs presents itself in enhancing the biological effect of focal irradiation through the use of systemic agents working as radiosensitizers. Several new drugs for the treatment of GBMs are being developed with the intention of achieving increased sensitivity to radiation; some of these agents may also exert cytotoxic activity on distant cell clones. These new drugs can be classified as hypoxic sensitizers, S-phase sensitizers, cytotoxic agents, and targeted agents to be used as sensitizers. Many of these agents have failed to demonstrate significant activity, but others are still under investigation. Briefly, hypoxic sensitizers, such as imidazole, efaproxiral, and tirapazamine, did not show a significant advantage when used in combination with EBRT in different Phase II trials; other agents, such as trans sodium crocetinate, are undergoing preclinical investigation. Disappointing results were also obtained with the S-phase sensitizers, such as bromodeoxyuridine, as well as for the cytotoxic agents including camptothecins, platinum agents, and taxanes. Different is the case for TMZ, an alkylating agent with activity in primary and recurrent gliomas; preclinical data have shown additive or even synergistic activity in combination with radiotherapy. Current data suggest that the most significant benefit with TMZ is gained from its activity as a radiosensitizer, and additional data indicate that even low doses have clinically significant activity with lower rates of toxicity.
going trials are investigating TMZ in combination with other novel chemotherapy, targeted, and radiosensitizing agents such as the epidermal growth factor receptor/tyrosine kinase inhibitor erlotinib and the platelet-derived growth factor/tyrosine kinase inhibitor imatinib.\textsuperscript{56,58} Possible efficacy has been demonstrated and studies of other biomolecular target agents are ongoing—for example, mTOR inhibitors (temsirolimus and RAD001),\textsuperscript{28} farnesyltransferase inhibitors (tipifarnib),\textsuperscript{17} antiangiogenesis agents (thalidomide and bevacizumab),\textsuperscript{4,82} and the oxidating agent motexafin Gd.\textsuperscript{50} Although markedly improved survival has not been associated with irradiation and radiosensitizers, this approach remains very attractive and worthy of further study.

**Conclusions**

Stereotactic radiosurgery and fSRT are noninvasive well-tolerated treatments that can be combined with chemotherapy or other adjuvant therapies. In patients with diagnostically established GBM, recurrent disease can be treated even if conventional fractionated radiotherapy (EBRT) has been used previously. To date, the majority of data published on SRS and fSRT for recurrent GBM have come from retrospective studies. Interestingly, all of these studies have suggested a survival benefit after SRS or fSRT for recurrent GBM, especially in younger patients with a good performance status\textsuperscript{33,66} and smaller tumors.\textsuperscript{44} As nonrandomized retrospective studies, however, these studies may have a selection bias toward patients whose treatment outcomes are more favorable.\textsuperscript{24} Prospective randomized trials are needed to discard this possibility. Nevertheless, the consistent finding of a survival benefit despite the varied selection criteria and treatment parameters in these retrospective studies is encouraging. Stereotactic radiosurgery and fSRT deserve further investigation for the management of recurrent GBM with the hope of increasing survival, reducing treatment side effects, and improving the quality of life for these patients.

**Disclaimer**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

**References**

2. Barker FG II, Chang SM, Gutin PH, Malec MK, McDermott
Role of stereotactic radiosurgery for recurrent GBMs


68. Souhami L, Seifheld W, Brachman D, Podgorsak EB, Wer...
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