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275 Comparison of Stereotactic Radiosurgery and Brachytherapy in the Treatment of Recurrent Glioblastoma Multiforme Clinical Study

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ABSTRACT: THE PURPOSE OF this study was to compare the efficacy of stereotactic radiosurgery (SRS) and brachytherapy in the treatment of recurrent glioblastoma multiforme (GBM). The patients had either progressive GBM or pathologically proven GBM at recurrence after previous treatment for a lower grade astrocytoma. Thirty-two patients were treated with interstitial brachytherapy, and 86 received treatment with stereotactic radiosurgery (SRS). The patient characteristics were similar in the two groups. Those patients treated with SRS had a median tumor volume of 10.1 cm³ and received a median peripheral tumor dose of 13 Gy. Patients treated with brachytherapy had a median tumor volume of 29 cm³. Median dose to the periphery of the tumor volume was 50 Gy delivered at a median dose rate of 43 cGy/hour. Twenty-one patients (24%) treated with SRS were alive, with a median follow-up of 17.5 months. Median actuarial survival, measured from the time of treatment for recurrence, for all patients treated with SRS was 10.2 months, with survivals of 12 and 24 months being 45 and 19%, respectively. A younger age and a smaller tumor volume were predictive of better outcome. The tumor dose, the interval from initial diagnosis, and the need for reoperation were not predictive of outcome after SRS. Five patients (16%) treated with brachytherapy were alive, with a median follow-up of 43.3 months. The median actuarial survival for all patients treated with brachytherapy was 11.5 months. Survivals of 12 and 24 months were 44 and 17%, respectively. The age of the patient (but not tumor volume, interval from initial diagnosis, or tumor dose) was predictive of outcome in these patients. A comparison of the results between patients treated with SRS and brachytherapy indicated a similar survival rate. Nineteen patients (22%) required reoperation after SRS, compared with 14 (44%) in the brachytherapy group. The actuarial risk for reoperation was 33% at 12 months and 48% at 24 months after SRS, compared with 54 and 65%, respectively, after

brachytherapy ($P = 0.195$). Those patients undergoing reoperation after brachytherapy survived longer than similar patients not undergoing reoperation. The outcome after SRS was independent of a need for reoperation. The treatment of recurrent GBM with SRS resulted in a survival rate similar to that obtained with interstitial high-activity ¹²⁵I implantation. This outpatient procedure is currently the treatment of choice for recurrent GBM at our institution in patients whose disease is amenable to SRS.

KEY WORDS: Brachytherapy; Radiosurgery; Recurrent glioma

Malignant gliomas comprise the majority of primary brain tumors in adults. Studies have identified a variety of biological and treatment-related prognostic indicators for patients with these aggressive neoplasms. For example, small postoperative residual tumor volume⁽²⁹⁾ and the use of adjuvant radiotherapy⁽²⁶⁾ and chemotherapy⁽⁷⁾ favorably influence outcome. Although standard treatment approaches can prolong life, they have had little impact on survival. Approximately half of the patients with glioblastoma multiforme (GBM) suffer recurrence and die within 1 year of diagnosis, and survival beyond 2 years is relatively rare. Likewise, patients with anaplastic astrocytomas recurring after primary treatment have a life expectancy of only several months⁽¹³⁾.

At the time of recurrence, treatment options are limited by the tumor location and size and the overall condition of the patient. A minority of patients may be candidates for reoperation, but prolonged survival is rare with this approach alone⁽³⁰⁾. Systemic chemotherapy may offer transient regression or stabilization of disease in some patients, despite substantial toxicity⁽¹⁴⁾. Retreatment of recurrent gliomas with standard external beam radiotherapy carries an unacceptable risk of injury to normal brain⁽²⁷⁾.

In recent years, new treatment options of focal radiation dose escalation have become available as a result of advances in radiographic imaging and three-dimensional computer analysis. Stereotactic brachytherapy has a proven role in the treatment of primary GBM (combined with surgery and external beam radiotherapy) and recurrent malignant gliomas^(18,23,24). More recently, stereotactic radiosurgery has proven to be a useful adjunct to surgery and external beam radiotherapy in the treatment of primary malignant gliomas⁽¹⁶⁾.

Radiosurgery may offer some advantages over brachytherapy in the treatment of recurrent GBM, requiring a single day of outpatient therapy, compared with the usual 6 to 7 days of hospitalization associated with interstitial brachytherapy⁽²⁾. We report our experience with radiosurgical treatment of recurrent GBM and compare the results with those obtained with interstitial brachytherapy at our institution.

PATIENTS AND METHODS

Patient characteristics

Between December 1, 1985 and July 1, 1993, 118 patients were treated for recurrent GBM at the Brigham and Women's Hospital. These patients had either an initial diagnosis of GBM and failure after primary treatment or had biopsy-proven GBM after failure of treatment for a lower grade astrocytoma (Table 1).

Eighty-six patients received treatment with stereotactic radiosurgery (SRS), and 32 were treated with interstitial ^{125}I implantation. Patient characteristics (Table 1) were similar in the two groups, with the exception of tumor volume. Median tumor volumes were 10.1 and 29 cm^3 for SRS and brachytherapy, respectively. Initially, brachytherapy represented standard therapy for these recurrent tumors, with SRS being reserved for smaller tumor volumes, tumors in nonimplantable sites (deep grey structures, brainstem, or eloquent cortex), or patients who were thought to be at increased risk for brachytherapy-related complication or who refused brachytherapy. However, with further experience, SRS became the preferred treatment for recurrent GBM, except in the case of larger or irregularly shaped volumes. Sixty-three percent of brachytherapy patients were treated before 1990. Ninety percent of the patients receiving SRS were treated since the beginning of 1990.

All of the patients had received previous external beam radiotherapy. Twenty-eight patients (33%) in the SRS group had received chemotherapy, compared with two patients (6%) in the brachytherapy group. Seven patients in the brachytherapy group had received etanidazole (SR 2508) as a radiosensitizer as part of their initial treatment protocol. Eight patients treated with SRS for recurrence had previous ^{125}I implantation as part of the initial therapy.

Brachytherapy

The details of the interstitial implantation have been described previously⁽¹⁷⁾. Briefly, ^{125}I sources (Model 6702, Medical Products Division, 3M Co., St. Paul, MN) were placed under local anesthesia using stereotactic guidance to deliver 34 to 100 cGy/hour (median, 43 cGy/hr) to the periphery of the enhancing tumor volume, including a 0.5-cm margin. Postimplant orthogonal plane radiographs were taken to obtain precise dosimetry. Total brachytherapy doses were 38.7 to 63.6 Gy (median, 50 Gy), delivered over a period of 50 to 137 hours (median, 119 hr). The tumor volumes treated with brachytherapy measured 5 to 83 cm^3 (median, 29 cm^3).

Stereotactic radiosurgery

Radiosurgery was performed using a dedicated 6 MV linear accelerator (Clinac 600 RS, Varian Associates, Inc. Palo Alto, CA) as an outpatient procedure for nearly all of the patients. The equipment and procedures used have been previously described in detail⁽¹²⁾. Briefly, the Brown-Roberts-Wells stereotactic head frame (Clinac 600 RS, Varian Associates, Inc.) was placed while the patient was under local anesthesia. A computed tomographic

(CT) scan with contrast was obtained with the head frame in place. The CT information was transferred to the treatment planning computer, and the relevant normal anatomy and tumor volumes of the patient were outlined. Using dedicated software (XKnife 2, Radionics, Inc., Burlington, MA), a treatment plan was designed consisting of a series of noncoplanar arcs through one to four isocenters, using one to three different diameter collimators (17.5-50 mm; median, 37.5 mm). Doses were prescribed to the isodose distribution that covered the enhancing tumor volume with a minimal 2- to 4-mm margin. The dose was normalized to the 50 to 100% isodose contour (median, 80%). Eighty-five percent of the treatments were prescribed with normalization to the 80 to 100% isodose volume. A single isocenter was used for 55% of the patients, and two isocenters were used in an additional 35%. Minimum peripheral doses of 6 to 20 Gy (median, 13 Gy) were delivered to volumes of 2.2 to 83 cm^3 (median, 10.1 cm^3).

On the day of treatment, anticonvulsant medication levels were evaluated and adjusted as needed. In addition, patients with large, deep-seated lesions received intravenous or oral high-dose steroids before, and for at least 2 days after, SRS.

Survival analysis

Follow-up was obtained in the multidisciplinary Brain Tumor Clinic or through referring physicians. CT or magnetic resonance imaging (MRI) scans were obtained every 3 months after treatment or more often if indicated. All radiographs were reviewed by members of the radiosurgery team. When indicated, $^{201}\text{Th}/^{99\text{m}}\text{Tc}$ single-photon emission tomography or positron emission tomography were obtained to distinguish between radionecrosis and recurrent tumor⁽⁴⁾.

A computerized database was compiled using all of the available patient data. The actuarial survival rate from the first day of brachytherapy or the date of radiosurgery was calculated using the Kaplan-Meier method⁽¹¹⁾. The survival data of different subgroups of patients were compared using the Mantel-Haenszel log-rank test⁽²⁰⁾. A multivariate analysis was performed using the Cox proportional hazards model⁽⁵⁾. Statistical analyses were performed in February 1994. Full follow-up was available on all living patients.

Reoperation after SRS or brachytherapy for recurrent GBM

A craniotomy for the resection of necrotic tissue and/or tumor was performed as clinically indicated by exacerbation of focal neurological symptoms related to increased intracranial pressure, increasing enhancement, and edema on computed tomography or MRI and steroid dependency. There were no specific criteria to indicate the need for reoperation. The decision to perform reoperation was individually made for each patient based on clinical and radiographic findings.

RESULTS

Survival after SRS or brachytherapy for recurrent

GBM

Twenty-one of 86 patients (24%) treated with SRS for recurrent GBM were alive, with a median follow-up of 17.5 months (range, 6.8–45.1 mo). The median actuarial survival, measured from the time of SRS was 10.2 months. Survivals at 12 and 24 months were 45 and 19%, respectively (*Fig. 1A*). Five of 32 patients (16%) treated with brachytherapy were alive, with a median follow-up of 43.3 months (range, 8.3–64.4 mo). The median survival for all of the patients treated with brachytherapy was 11.5 months, measured from the day of implantation; survivals at 12 and 24 months were 44 and 17%, respectively (*Fig. 1B*). Comparison of results achieved with SRS and brachytherapy indicated similar median survivals of 12 and 24 months ($P = 0.555$).

Factors affecting survival of patients with recurrent GBM

Patient age and gender, tumor volume, interval from initial diagnosis, and treatment dose were examined as potential prognostic factors for the groups of patients treated with either brachytherapy or SRS. For patients treated with SRS, age and tumor volume were significantly predictive of outcome on univariate analysis. 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 (*Fig. 2*) ($P = 0.005$). Those patients with tumor volumes smaller than 10.1 cm³ also survived longer after SRS than patients with larger tumors; median survivals were 15.1 and 8.1 months, respectively (*Fig. 3*) ($P = 0.007$). A young age and a small tumor volume remained positive prognostic factors on multivariate analysis (relative risk, 0.829 and 0.707, respectively; $P < 0.005$). Patient gender, tumor dose, and interval from initial diagnosis to recurrence were not predictive of outcome in patients treated with SRS. Patient age, but not tumor volume, interval from diagnosis to recurrence, or tumor dose, was predictive of outcome in patients treated with brachytherapy. The median survival was 16.4 months for patients less than 46 years old, compared with 9.0 months for older patients (*Fig. 4*) ($P = 0.004$).

Patterns of failure after SRS or brachytherapy

Failures were classified as in previous studies⁽¹⁷⁾: 1) local, enlargement of contrast-enhancing tumor not more than 2 cm from original tumor volume; 2) marginal, failure greater than 2 cm but no more than 5 cm from original tumor volume; 3) distant, failure greater than 5 cm from the original tumor volume, contralateral hemisphere, spine, or extraneural sites.

Eighty-four of 86 patients (98%) treated with SRS were able to be evaluated for patterns of recurrence. Two patients surviving less than 1 month after treatment were excluded from this analysis. Sixty-eight of these 84 (81%) have failed at the time of analysis (*Table 2*). Of the 68 failures, 21 (31%) were local, 33 (48%) marginal, and 14 (21%) distant.

Twenty-six patients treated with brachytherapy were able to be evaluated for patterns of recurrence. Twenty of these patients have experienced failures (*Table 2*). Of the 20 failures, 6 (30%) were local, 10

(50%) marginal, and 4 (20%) distant.

Complication of SRS and brachytherapy

Acute complications after SRS were infrequent and generally mild. One patient developed *Pneumocystis carinii* pneumonia 1 month after SRS, presumably secondary to steroids⁽²⁵⁾. Three patients on anticonvulsants for previous seizures experienced seizures within 24 hours after treatment, possibly as a result of acute swelling from radiosurgery. Two patients required hospitalization in the days after SRS. One of these suffered acute herniation secondary to edema and died after radiosurgery for a 39.6-cm³ mesial temporal lobe lesion. The second developed hydrocephalus and required a ventricular shunt. Two patients had transient aphasia, and two developed transient motor deficits.

Late complications (more than a month after treatment) after SRS were attributable to necrosis of tissue within the target volume or late cranial nerve damage. Radionecrosis was generally manifested in the first 2 to 4 months after treatment by headache, nausea, and exacerbation of preexisting neurological abnormalities. Radiographic findings consisted of increasing contrast enhancement and edema on a CT scan. Although most patients promptly improved with steroids, 19 (22%) of the 86 patients in the SRS group failed to respond and required craniotomy for resection of necrotic tumor (see below). One patient developed ptosis secondary to cranial nerve III damage 11 months after SRS.

The acute complications of brachytherapy were limited to two scalp infections. The late complications included the development of homonymous quadrantanopsia in two patients with deep temporal lobe lesions. The major late effect of brachytherapy is associated with focal necrosis and edema and neurological deterioration. This is the major indication for reoperation (see below).

Reoperation after treatment for recurrent GBM

Nineteen patients (22%) underwent reoperation after SRS, compared with 14 (44%) in the group treated with brachytherapy. The actuarial risk of undergoing reoperation was 33% at 12 months and 48% at 24 months after SRS, compared with 54 and 65%, respectively, after brachytherapy (*Fig. 5*) ($P = 0.195$). Patients undergoing reoperation after brachytherapy survived longer than similar patients not undergoing reoperation. Median survival for the 14 patients undergoing reoperation after brachytherapy was 19.2 months, compared with 8.5 months for patients not undergoing reoperation (*Fig. 6A*) ($P = 0.003$). There was also a long-term survival advantage for patients undergoing reoperation after brachytherapy; survivals of 12 and 24 months were 84.6 and 23.1%, compared with 12.1 and 6.1% for those patients not undergoing reoperation, respectively. The patients had similar survivals after SRS irrespective of whether reoperation was performed (*Fig. 6B*) ($P = 0.229$).

Histopathological examination of the material resected at reoperation revealed various amounts of necrotic tissue and apparent tumor cells. All 14

reoperation specimens from the patients treated with radiosurgery contained both necrosis and tumor cells. Seventeen of 19 (89%) specimens from reoperation after brachytherapy contained tumor; two specimens contained tumor only, and two showed only radionecrosis. There was no correlation between findings at reoperation and eventual outcome (data not shown).

DISCUSSION

More than 95% of the patients with primary GBM fail initial therapy of surgery and external beam radiotherapy with or without adjuvant chemotherapy (22,26). The vast majority of recurrences are focal at the initial site of the disease (28). Although there has been a prolongation of the duration of local control after an aggressive boost treatment with brachytherapy (18,23,24) or SRS (16), the vast majority of patients with GBM do not receive these aggressive treatments. Local and marginal failures continue to be the predominant mode of recurrence in this group of patients.

Despite this, chemotherapy has historically been the standard therapy for recurrent malignant gliomas. Levin et al. (15) report a 55% response rate and a median time to progression of 23 weeks for patients with recurrent GBM treated with combination chemotherapy.

Local therapy with surgery alone has been reported to offer a median survival of 29 to 36 weeks for recurrent GBM (3,9,30). Cumulative operative and postoperative mortality approaches 10% (9). More recently, implantation of ¹²⁵I seeds for recurrent GBM has been shown to offer excellent palliation in a majority of patients and a significant level of long-term survival. Gutin et al. (8) compared the survival of an initial group of 18 patients treated with ¹²⁵I implant for recurrent GBM with 42 matched historical controls treated with chemotherapy. Median survival was 28 weeks for the group of patients treated with chemotherapy, compared with 52 weeks for the implanted group. Leibel et al. (13) reported on 45 patients with recurrent GBM treated with high activity ¹²⁵I implantation. A median survival of 54 weeks from the time of implantation was achieved. Eight percent survived 3 years, and two patients were reported to have survived more than 6 years. A recent update of the University of California, San Francisco series by Scharfen et al. (23) reported a 49-week median survival and 15% 3-year survival after brachytherapy in 66 patients with recurrent GBM.

Stereotactic radiosurgery has become increasingly available in the United States in recent years and may have several advantages over brachytherapy as a means of delivering high-dose focal radiotherapy (2). Radiosurgery is a 1-day procedure that can usually be accomplished as an outpatient procedure. Many of the risks involved with brachytherapy (for example, infection, hemorrhage, exposure of personnel to radiation) do not apply to radiosurgery. Radiosurgery is also a treatment option in patients with deep-seated lesions not usually considered implantable. Therefore, in many centers having the capability to do either procedure, SRS has become the treatment of

choice of recurrent GBM.

The data presented here indicate that SRS and brachytherapy offer equivalent efficacy in the treatment of recurrent GBM in terms of median 1- and 2-year survivals (Fig. 1). The median survivals of 10.1 and 11.5 months for SRS and brachytherapy, respectively, compare well with those reported by others after brachytherapy (13,23,24). Although this represents a retrospective comparison, the two groups of patients did not differ substantially (Table 1), except that the brachytherapy-treated group included a higher proportion of patients with larger tumor volumes. However, restricting analysis to patients with larger tumor volumes (≥ 30 cm³) did not reveal any significant difference between survival of the patients treated with brachytherapy (n = 15) and those treated with SRS (n = 12) (Fig. 7) ($P = 0.217$).

The complications after brachytherapy in this series of patients were similar to those reported by others (23,24). The acute complications were limited to scalp infections in two patients. The late complications were associated with focal necrosis and edema and with neurological deterioration. This is the major indication for reoperation, which was required in nearly half of the patients implanted. This rate of reoperation is similar to that found by Scharfen et al. (23) in a similar group of patients with recurrent GBM.

The complications related to treatment of recurrent GBM with SRS are similar to those described after brachytherapy. The acute complications are related to edema and are manifest as a worsening of pre-existing symptoms (seizure, aphasia, motor deficits). These were treated with steroids and were transient in the majority of cases. Two patients suffered acute edema, becoming symptomatic soon after SRS, and required hospitalization. One of these patients with a deep temporal lobe lesion (volume 39.6 cm³) had progressive deterioration of mental status despite aggressive therapy. She died secondary to herniation on the second day after SRS. The second patient was treated for a 3.7-cm³ frontal lesion and developed hydrocephalus requiring shunt placement on the day after radiosurgery. The life-threatening acute complications (seizure, acute edema, pneumonia) occurred in 6 of 86 (7%) patients treated with SRS. This is not different from the rate reported by the group at the University of California, San Francisco after brachytherapy (7.2%) (23). The late effects included the need for reoperation in 22% of the patients. In addition, one patient developed a permanent third cranial nerve palsy manifested by ptosis.

The patterns of failure were similar after brachytherapy or SRS as treatment for recurrent GBM, with most patients experiencing local or marginal failure (Table 2). These findings are similar to those reported after brachytherapy as a boost after external beam radiotherapy for primary GBM (1,17,24). The equal distant-failure rates for both the SRS and brachytherapy patients suggest that the brachytherapy procedure itself does not lead to diffuse tumor seeding, as some have suggested (10).

The rates of reoperation were also similar between

the two groups. The actuarial risk of reoperation for patients surviving 1 year were 38 and 54% for SRS and brachytherapy, respectively. Evaluation of follow-up CT or MRI scans after high-dose brachytherapy is difficult^(6,8). Distinguishing radionecrosis from recurrent tumor in the months after radiosurgery is equally difficult. Daumas-Duport et al.⁽⁶⁾ found that tissue taken from the high-dose region after interstitial brachytherapy was not predictive of recurrence because of the difficulty of distinguishing reactive gliosis from the presence of tumor cells, the viability of which is not known. Single photon emission computed tomography and positron emission tomography have been used with some success in establishing whether radiographic changes constitute recurrence or radiation effect. However, even when all evidence indicates radiation necrosis, craniotomy and removal of necrotic tissue are often needed to relieve symptoms. Some evidence of tumor cells is identified in >90% of such reoperation specimens⁽²³⁾.

Survival in patients undergoing reoperation after brachytherapy has been reported to be improved, compared with similar patients not undergoing reoperation (*Fig. 6A*)^(23,24). Although patients in our series undergoing reoperation after SRS also had prolonged median survival compared with patients not having reoperation (14.8 versus 8.2 mo), this difference was not statistically significant (*Fig. 6B*). It is not clear whether reoperation is therapeutic in terms of tumor control or whether the need for reoperation is related to response of the tumor to high radiation dose. In either case, reoperation remains a necessary component of the treatment of patients with high-dose focal radiation.

The treatment of patients with recurrent GBM using SRS resulted in survival similar to that obtained with stereotactic brachytherapy. The patterns of recurrence and rates of complication were also similar between the groups of patients undergoing either of these two therapies. SRS has several advantages over brachytherapy: it is usually accomplished as a single-day outpatient procedure; patients who would not be candidates for brachytherapy because of deep tumor location are not precluded from treatment with SRS; there is little risk of infection or hemorrhage after SRS.

Although both brachytherapy and SRS offer excellent palliation for recurrent GBM, few, if any, patients are cured. Because local failure remains a major problem, it may be reasonable to add a pyrimidine analog or hypoxic cell radiosensitizer⁽¹⁹⁾ to SRS for these tumors. Because SRS is a single treatment, the logistics of administration over a prolonged course of therapy and the toxicity associated with high cumulative doses of these radiosensitizers may be avoided.

Currently, we recommend that patients with small, radiographically distinct and focally recurrent GBM be considered for stereotactic radiosurgery. Larger lesions (>30 mm diameter), especially those adjacent to eloquent cortex or critical white matter pathways, must be evaluated with caution. The potential for acute toxicity associated with radiosurgery increases

substantially for larger lesions⁽²¹⁾. At our institution, patients with lesions greater than 30 mm in diameter selected for treatment with radiosurgery are hospitalized overnight for observation.

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COMMENTS

This article reports two separate retrospective studies of patients with recurrent glioblastomas, one group treated with brachytherapy and the other with stereotactic linear accelerator radiosurgery. The treated groups are disparate in terms of median tumor volume (10.1 versus 29 cm³) and in terms of median follow-up (17.5 versus 43 mo), so the attempted comparison of the results of the treatments is questionable. The authors try to ameliorate the disparity in tumor sizes by comparing the results of only those subgroups of patients who received the

two treatments for tumors greater than 30 cm³. Although the results of the two treatments were not different in these groups, it is difficult to interpret just how comparable the two groups were without knowing the median tumor volumes of both. In addition, the longer follow-up of the patients treated with brachytherapy would worsen the results in this group and, therefore, bias the comparison. Other major differences between the two groups that favor the results of the radiosurgery trial include the number of patients treated for malignant glioma who actually started with low-grade tumors and the interval from initial treatment to treatment at relapse. In addition, early in the radiosurgery trial, patients were selected for small tumor size or for other criteria that were not applied to patients treated with brachytherapy.

The comparison between brachytherapy and radiosurgery made by these authors is invalid for the reasons given above. Each modality undoubtedly has its place in the management of patients with difficult tumors, but a direct comparison of their efficacy must await a randomized trial with selection criteria that level the playing field.

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The authors present important data on the clinical course and patterns of failure in 118 patients with recurrent malignant glioblastoma in an attempt to compare the efficacy of interstitial brachytherapy with stereotactic radiosurgery. This sophisticated and detailed retrospective study highlights many of the difficulties involved in reaching a conclusion based on nonrandomized, noncontemporaneous data.

The authors claim (in *Table 1* of the article) that the patient characteristics of the 32 brachytherapy patients are essentially the same as those of the 86 undergoing radiosurgery. They admit that the treatment volumes in the brachytherapy group (median, 29 cm³) are greater than those in the radiosurgery group (median, 10.1 cm³). However, *Table 1* of the article also indicates that the brachytherapy group is heavily weighted toward males (75 versus 61%), and, more importantly, toward tumors that were GBMs or anaplastic astrocytomas at initial presentation rather than low-grade tumors at first treatment (94 versus 88%). Moreover, the median interval from initial diagnosis was only 7.3 months in the brachytherapy group, possibly indicating a more malignant clinical course; it was 10.3 months in the radiosurgery group. Despite these differences, the long-term outcomes were essentially the same.

Because 63% of the brachytherapy patients were treated before 1990, their median length of follow-up is 43.3 months and there should be little or no censored data in the survival curve. Note that after 1990, brachytherapy was reserved for patients with large and irregular lesions (a treatment bias) and that 90% of the patients undergoing radiosurgery were treated after this date. As a consequence, the median follow-up in the radiosurgery group is only 17.5

months. Another problem with comparing two groups of patients treated in two different eras is that advances in computerized treatment planning after 1990 were not available for brachytherapy patients before 1990.

The authors state that they did not have a uniform policy on reoperation and assert that only "a minority of patients may be candidates for this approach." Nevertheless, those patients undergoing both brachytherapy and reoperation represented their most favorable prognostic group (median, 19.2 mo; survival of 24 mo, 23.1%). This corroborates the experience of Gutin and colleagues⁽²⁾. The use of rescue therapies for recurrent brain tumors in different clinics is highly variable. A uniform policy regarding reoperation can result in a surgical rate as high as 58%, irrespective of many patient and tumor characteristics, with a median survival of 9 months⁽³⁾. The use of reoperation before implantation or radiosurgery might have equalized the volumes of some of the patients included in this study; reoperation almost certainly would have prevented the acute deterioration observed in two of the radiosurgery patients. In any event, the use of either brachytherapy or radiosurgery in a given patient is equally subject to selection bias. It is estimated that only one-fourth to one-third of all patients are eligible for such treatments and that many of their clinical characteristics are inherently superior to those of patients seen in nonreferral centers⁽¹⁾.

Although the patterns of failure (*Table 2* of the article) and the median survivals were similar after both brachytherapy and radiosurgery, it is not clear that the biological effect of 50 Gy given over 119 hours is the same as that of 13 Gy given over a few minutes. Survival in both groups of patients was age dependent but was volume dependent only in the case of radiosurgery, and the incidence of reoperation was much higher in the brachytherapy group. One way to interpret these data is to conclude that it is much easier to bring a patient to the edge of biological tolerance with brachytherapy than it is with radiosurgery. It may also be easier to treat large volumes with brachytherapy and to couple such treatment with an immediately preceding reoperation. Given some of the bias built into the present study, one might even conclude that brachytherapy, cheaper and easier to implement in the average hospital, is at least as good as or superior to radiosurgery in a larger cross-section of patients. In the present socioeconomic environment, can we really afford the technological and personnel costs involved in the use of radiosurgery to produce marginal benefits in relatively few patients? Can we even afford the randomized trial that might tell us who those patients are?

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The use of intensive local therapy for recurrent glioblastoma has provided an improved survival rate in select patients with recurrent glioblastoma. The two most often used methods of re-irradiation (stereotactic radiosurgery or brachytherapy) extends survival for several months in patients who are candidates for these treatments. Consequently, comparison of these treatments is an important contribution. Although the patients in the two treatment arms in this report are not precisely comparable, the similarities in age and Karnofsky status, etc., suggest that a comparison in their outcomes is reasonable. Because the mean tumor volume in brachytherapy patients was three times the volume in stereotactic radiosurgery (SRS) patients, one would anticipate that these patients would respond less favorably. Tumor volume has a predictive value in determining the outcome for SRS patients but not for brachytherapy patients. However, restricted analysis of patients with the largest volumes ($\geq 30 \text{ cm}^3$) show no difference in survival with either form of treatment. It would be interesting to examine whether there is a difference in tumors with other volumes (greater than the SRS mean of 10.1 cm^3 and less than 30 cm^3).

The discussion on the pattern of failure in these patients is important. Approximately 70% of the patients from each group fail outside the margin of treatment. This failure pattern is predictable, because the volume of therapy is determined by treating the region of abnormal blood-brain barrier (contrast enhancement) rather than the true extent of tumor invasion beyond this radiographically defined margin. This raises the question of whether the addition of an hypoxic cell radiosensitizer, as suggested by the authors, would be of benefit, because treatment failure appears to be the result of inadequate irradiation of invasive tumor rather than radioresistance of hypoxic tissue.

The use of SRS and other expensive devices for the treatment of brain tumors needs close examination, and studies of efficacy and appropriate application of this technology are important. Careful patient selection and rigorous follow-up evaluations are two reasons why the Joint Center for Radiation Therapy

has been a valuable source for objective data from which we can all benefit.

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The authors have performed a retrospective analysis of their experience with boost radiation techniques in the management of patients with progressive glioblastoma multiforme, despite multimodality prior therapies. I think that their tentative data supports the concept that stereotactic radiosurgery may enhance the survival of appropriately selected glioblastoma patients and may provide results with fewer risks superior to those obtained by brachytherapy. There are several cautions related to this interpretation. Preselection bias of the patients is obvious, and even the authors changed their minds during the course of this study, as witnessed by the number of patients who subsequently underwent radiosurgery as opposed to brachytherapy boost. The patients were not stratified by tumor volume or location. These two features (and, usually, age) are tremendously important stratification variables, which, in advance, may help predict the outcomes of patients with glioblastomas regardless of the therapeutic option delivered. To date, most studies reporting to show significant benefits in therapy are confounded by these variables, and, therefore, such pressing questions as the role of surgical cytoreductive efforts, tumor therapeutic trials, radiation dose, and delivery are confusing. The use of boost irradiation techniques is logical, because most prior efforts in the management of glioblastoma have identified that the single therapeutic variable that most effects survival is the delivery of an appropriate dose of radiation therapy.

Patients who underwent boost radiation techniques at this center had significantly smaller tumor volumes if they had stereotactic radiosurgery, as compared with brachytherapy. On the other hand, patients who underwent radiosurgery could also have deep tumors, which are usually not selected (and were not in this study) for brachytherapy. A better explanation of potential radiobiological effects is necessary in the future, especially as we analyze the equivalency of single-fraction radiosurgery, the role of stereotactic fractionated external beam radiation therapy, and conventional radiosurgery in this group of patients. In the future, we also need to better understand how "conformal" the radiosurgery treatment planning must be in order to result in a positive effect for glioblastoma. It is of significant interest that patients who underwent radiosurgery required fewer re-operations than those who underwent brachytherapy, but this feature alone may be accounted for by the significant difference in tumor volumes. Patients with small tumor volumes are less likely to require subsequent resection if the tumor is controlled. The presence of residual tumor cells is not surprising, but the issue of cell viability versus cell division capability is yet to be understood both in vivo and in vitro.

These studies do support the concept that at centers

of excellence, stereotactic radiosurgery may provide another means of significantly improving survival in glioblastomas. Their data is in agreement with our data, which indicate that the 24-month survival of patients with glioblastoma who completed histological diagnosis, up-front chemotherapy with continuous infusion of carmustine and cisplatin, fractionated external beam radiation therapy, and a stereotactic radiosurgical boost had a 40% 2-year survival.

Multicenter appropriately stratified trials will help to enhance the evaluation of these technologies. Studies such as this provide the framework from which to ask even more serious questions in the future.

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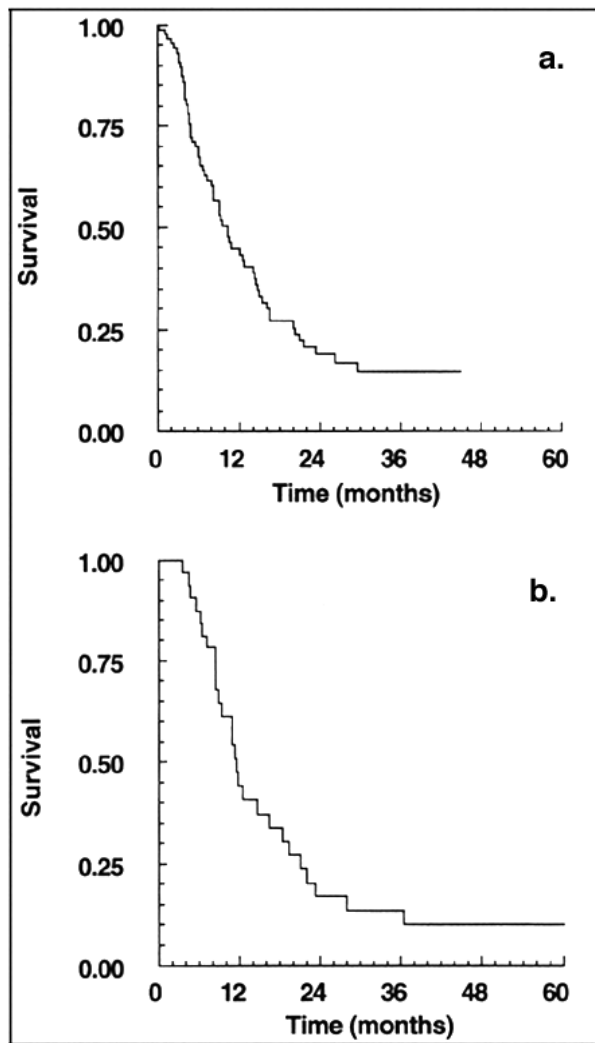


Figure 1. Survival of patients with recurrent GBM after SRS (A) or brachytherapy (B).

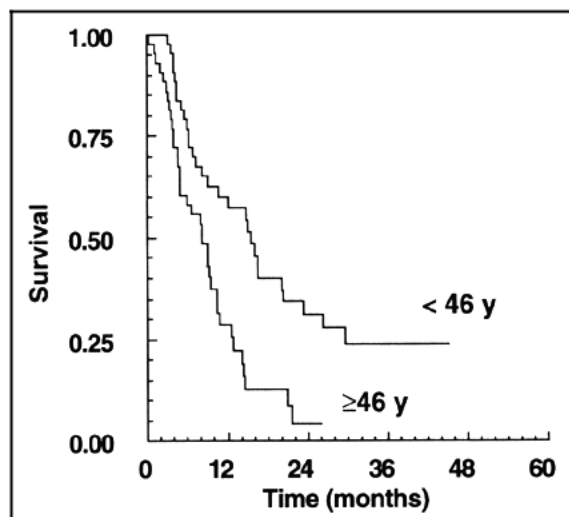


Figure 2. Survival after radiosurgery for recurrent GBM according to patient age.

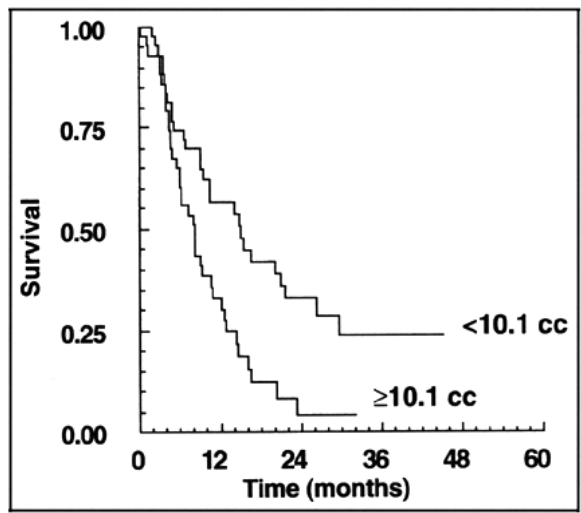


Figure 3. Survival after radiosurgery for recurrent GBM according to tumor size.

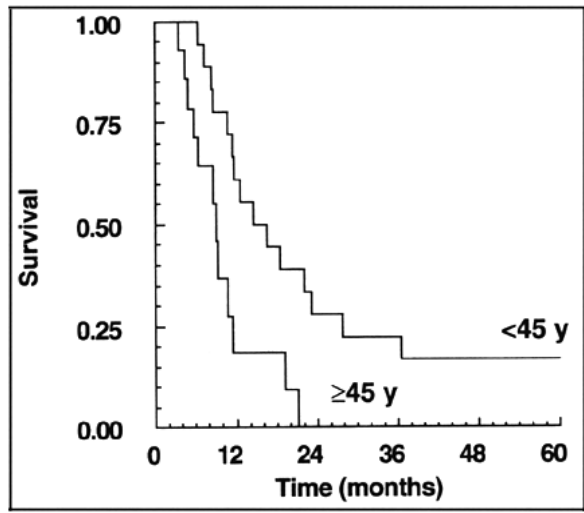


Figure 4. Survival after brachytherapy for recurrent GBM according to patient age.

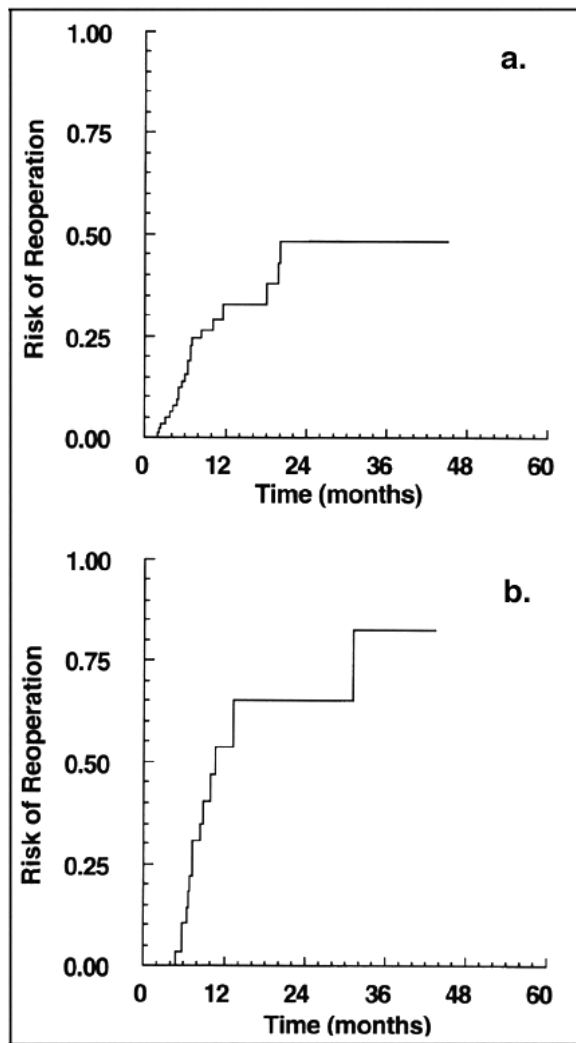


Figure 5. Risk of reoperation as a function of time after SRS (A) or brachytherapy (B) for recurrent GBM.

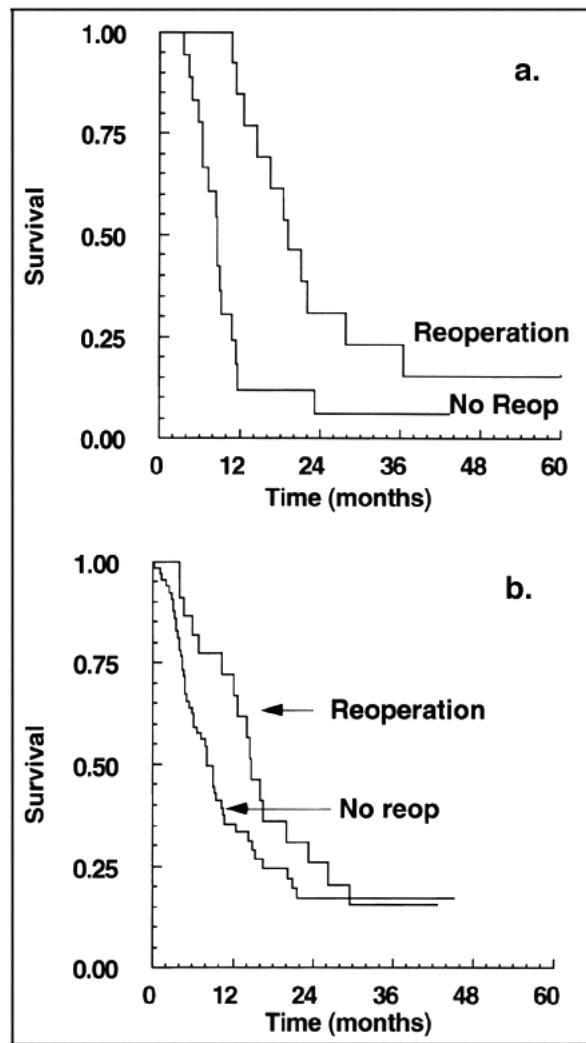


Figure 6. Effect of reoperation after treatment for recurrent GBM with brachytherapy (A) or SRS (B). Reop, reoperation.

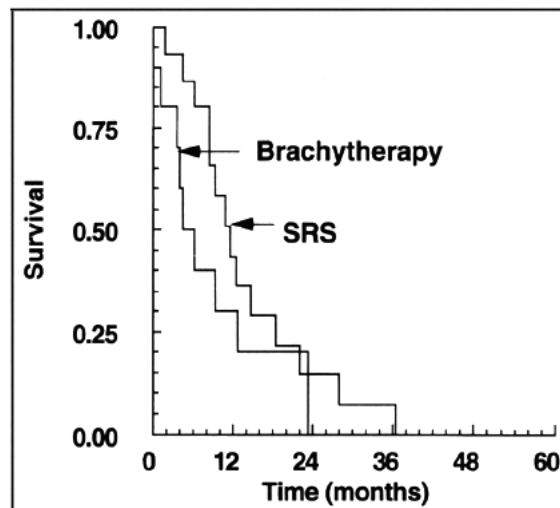


Figure 7. Survival of patients with recurrent GBM and tumor volume $>30 \text{ cm}^3$ after brachytherapy or SRS.

Characteristic	Radiosurgery (n = 86)	Brachytherapy (n = 32)
Age		
Range	9–77 yr	9–70 yr
Median	46 yr	45 yr
Gender (No. of patients)		
Male	53	24
Female	33	8
Interval from initial diagnosis		
Range	2.3–115 mo	1.5–54 mo
Median	10.3 mo	7.3 mo
Initial histology (No. of patients)		
Glioblastoma multi-forme	72	28
Anaplastic astrocytoma	4	2
Low grade astrocytoma	10	2
Site (No. of patients)		
Frontal	35	13
Parietal	15	6
Temporal	21	13
Occipital	4	1
Cerebellar	3	0
Deep structures	8	0
Tumor volume		
Range	2.2–83 cm ³	5–83 cm ³
Median	10.1 cm ³	29 cm ³
Karnofsky performance status		
Median	80	80
Range	40–100	50–100

Table 1. Patient Characteristics

Treatment	No. Patients	No. Failures (%)	Pattern of Failure		
			Local	Marginal	Distant
Stereotactic radiosurgery	84	68 (81)	21 (31)	33 (49)	14 (20)
Brachytherapy	26	20 (77)	6 (30)	10 (50)	4 (20)

Table 2. Patterns of Failure after Treatment for Recurrent Glioblastoma Multiforme