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CLINICAL INVESTIGATION **Brain**

RANDOMIZED COMPARISON OF STEREOTACTIC RADIOSURGERY FOLLOWED BY CONVENTIONAL RADIOTHERAPY WITH CARMUSTINE TO CONVENTIONAL RADIOTHERAPY WITH CARMUSTINE FOR PATIENTS WITH GLIOBLASTOMA MULTIFORME: REPORT OF RADIATION THERAPY ONCOLOGY GROUP 93-05 PROTOCOL

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Purpose: **Conventional treatment of glioblastoma multiforme (GBM) cures less than 5% of patients. We investigated the effect of stereotactic radiosurgery (SRS) added to conventional external beam radiation therapy (EBRT) with carmustine (BCNU) on the survival of patients with GBM.**

Methods and Materials: **A total of 203 patients with supratentorial GBM (tumor ≤40 mm) were randomly assigned either to postoperative SRS followed by EBRT (60 Gy) plus BCNU (80 mg/m^2 Days 1–3 every 8 weeks for six cycles) or to EBRT with BCNU alone. The dose of radiosurgery was tumor size–dependent and ranged from 15 Gy for largest to 24 Gy for smallest tumors. RT and BCNU were identical in both arms.**

Results: **At a median follow-up time of 61 months, the median survival in the radiosurgery group was 13.5 months (95% confidence interval, 11.0–14.8) as compared with 13.6 months (95% confidence interval, 11.2–15.2, $p = 0.5711$) for the standard treatment group. There were also no significant differences in 2- and 3-year survival rates and in patterns of failure between the two arms. Quality of life deterioration and cognitive decline at the end of therapy, compared with baseline, were comparable and there was no difference in quality-adjusted survival between the arms.**

Conclusions: **Stereotactic radiosurgery followed by EBRT and BCNU does not improve the outcome in patients with GBM nor does it change the general quality of life or cognitive functioning.** **© 2004 Elsevier Inc.**

Stereotactic radiosurgery, Radiation therapy, Glioblastoma multiforme, Quality of life.

INTRODUCTION

The management of patients with glioblastoma multiforme (GBM) is difficult and frustrating, because most patients succumb to the disease even when managed with the best contemporary therapeutic modalities. Radiation therapy remains the most effective adjuvant modality in the management of GBM and the overall survival time appears to be directly correlated with the total dose delivered (1, 2). Considering that 90% of recurrences are located within 2 cm of the enhancing edge of the original tumor (3) and that the occurrence of multicentric or metastatic disease is uncommon (4), a treatment delivering a localized high dose to the tumor with minimal irradiation of adjacent brain tissues

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should lead to an improved therapeutic ratio by increasing the local tumor control without an increase in the complication rate.

Stereotactic radiosurgery (SRS) is a radiotherapy technique characterized by accurate delivery of high doses of radiation in a single session to small intracranial targets in such a way that the dose fall-off outside the targeted volume is very sharp. Earlier institutional experiences showed encouraging median survival time results on several series of patients treated with a SRS boost in the initial management of malignant gliomas (5, 6). However, this apparent improvement in survival simply may have been related to patient selection rather than to a treatment effect from the SRS (7, 8).

To clarify this issue, the Radiation Therapy Oncology Group (RTOG) conducted a prospective, Phase III trial evaluating SRS boost in patients treated for GBM. This article reports the results of the RTOG protocol 9305, the first multi-institutional randomized trial comparing the use of SRS followed immediately by conventional external beam radiation therapy (EBRT) in one arm to only EBRT in the other arm. Carmustine (BCNU) chemotherapy was administered in both arms of the study.

METHODS AND MATERIALS

Study participants

Eligible patients were 18 years of age or older with a histopathologically proven diagnosis of supratentorial GBM. Patients with astrocytoma with atypical or anaplastic features were excluded. Further prerequisites included no prior cranial radiation or chemotherapy; a Karnofsky performance score (KPS) of 60 or higher; life expectancy of 3 months or greater; adequate bone marrow reserve; acceptable renal and hepatic function; and a normal chest X-ray. All patients required a diagnostic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scan performed preoperatively and postoperatively before initiation of radiation treatment, demonstrating a well-circumscribed lesion with a maximum dimension, in any direction, of $\leq$40 mm. Patients with tumor larger than 40 mm were eligible only when the tumor was rendered $\leq$40 mm after surgical resection. Only the residual tumor, as seen in the postoperative scan, was included in the radiosurgical target volume. Patients who had a gross total resection, with no visible tumor in the postsurgical scan were not eligible, irrespective of the initial tumor size. Patients with tumors that originated in the brainstem, or were located adjacently (within 5 mm) to the optic chiasm were not eligible. All patients signed a study-specific informed consent form.

Study design

The study was a prospective, randomized trial comparing EBRT plus BCNU (arm 1) to up-front SRS followed by EBRT plus BCNU (arm 2). Patients were stratified by age (younger and older than 50 years) and KPS (below and above 80). The primary endpoint was survival. Secondary endpoints were the determination of the frequency and severity of toxicities between regimens and a comparison of the treatment effects on neurologic function and quality of life.

Patients were evaluated with a detailed neurologic examination before the start of treatment and at each follow-up visit. The Mini-Mental Status Examination (MMSE) and the Spitzer QOL Index evaluated neurologic function and quality of life (QOL), respectively, both performed before therapy, during EBRT and at each follow-up visit. We used the standard error of measurement (SEM) to determine any meaningful change in scores. Contrast-enhanced CT or MRI scans were regularly done at 3- to 4-month intervals or at time of neurologic progression. Additionally, the KPS and dexamethasone dosage were recorded.

Participating institutions were required to fill out the RTOG stereotactic radiotherapy facility questionnaire based on a set of parameters previously established (9) and to receive subsequent approval of their stereotactic equipment and technique by the RTOG Quality Assurance Review Committee.

External beam radiation therapy or SRS were begun no later than 5 weeks after surgery. SRS was delivered 1 week before EBRT either by gamma knife or a linear accelerator (linac)-based radiosurgical technique.

The SRS dose was tumor size–dependent and was based on the RTOG protocol 9005 (10). Tumors up to 20 mm in maximum dimension received a dose of 24 Gy, tumors measuring 21–30 mm received 18 Gy, and tumors measuring 31–40 mm received 15 Gy. The dose was prescribed to the isodose surface (50% to 90%) encompassing the margin of the tumor, as defined by the imaging studies.

External beam radiation therapy was identical in both arms. One treatment of 2 Gy was given daily, 5 days per week for a total dose of 60 Gy. For the first 46 Gy, the treatment volume included the contrast-enhancing lesion and surrounding edema on the preoperative scan plus a 20-mm margin. After 46 Gy, the target volume included the presurgical contrast-enhancing lesion plus a 25 mm margin. If no surrounding edema was present, the initial target volume included the contrast enhancing lesion plus a 25 mm margin.

Carmustine was given intravenously at a dose of 80 mg/m^2 on Days 1, 2, and 3 of the first week of EBRT and repeated every 8 weeks for five cycles (maximum BCNU dose 1440 mg/m^2). BCNU administration was identical in both arms.

Quality control assessment

A physician and a medical physicist reviewed all submitted data to verify protocol compliance. The RTOG quality assurance guidelines (9) were used to assess adherence to the radiosurgery treatment protocol. The following parameters were evaluated. *(1)* The prescription dose. Any prescribed dose outside the protocol recommendation was considered a major violation. *(2)* The homogeneity index

defined by the ratio of the maximum dose divided by the prescription dose (MDPD). A ratio of ≤2.0 was per protocol. MDPD ratio >2.0 but <2.5 was considered a minor variation. MDPD ratio >2.5 was considered a major acceptable variation. *(3)* The conformity index defined by the ratio of the prescription isodose surface volume divided by the target volume (PITV). A ratio between 1.0 and 2.0 was considered per protocol. PITV ratio <1.0 but >0.9 was classified as minor deviation, whereas PITV ratio <0.9 was classified as major deviation. PITV ratio between 2.0 and 2.5 was classified as minor deviation, whereas PITV ratio >2.5 was considered a major acceptable deviation. *(4)* The appropriateness of the target volume coverage. If the 90% of prescription isodose line completely encompassed the target volume, the case was considered per protocol. If the 90% of prescription isodose line did not completely cover the target volume, but the 80% of prescription isodose line did, the case was classified as a minor deviation. If the 80% of prescription isodose line did not completely cover the target volume, the case was classified as a major acceptable deviation.

Statistical analysis

The trial was designed to demonstrate an improvement of 50% in median survival (12.5–18.75 months). These estimates were based on median survival times of patients receiving EBRT and BCNU enrolled on protocol RTOG 8302 (8) vs. median survival times of patients treated with a regimen of SRS plus EBRT and BCNU by Loeffler *et al.* (5). The estimated sample size of 200 patients would ensure an 80% probability of detecting the specified improvement, if it existed, while rejecting the null hypothesis at the 95% level ($\alpha = 0.05$, one-sided type I error).

The treatment allocation used a randomized permuted block within strata to balance for patient factors other than institution. The stratifying variables that were identified in a previous database analysis (11) were the age and KPS of the patients. Patients were excluded from analysis for the following reasons: ineligibility, consent withdrawn, dead or too ill before start of therapy, or tumor >40 mm at time of SRS. However, an intention-to-treat analysis of all randomized patients was also performed. Survival estimates were computed using the Kaplan-Meier method (12) and the two groups were compared using the log–rank test.

Patterns of failure were evaluated as the first reported site of failure. Time to tumor progression was estimated using a competitive risk model (13). The SEM was used to determine whether patients had improved, deteriorated, or remained stable at a follow-up time point compared with the preradiation baseline score. Differences in proportions of patients in these categories were compared using the Wilcoxon rank-sum test (14). Only patients with data both at baseline and at the follow-up time point were used. The reasons for missing observations are presented and no imputation for missing QOL or MMSE scores was performed.

RESULTS

Patient characteristics

Between February 1994 and June 2000, 203 patients were enrolled. Ten were deemed ineligible (five in arm 1; five in arm 2) because of anaplastic histology (3 patients), refusal of therapy or withdraw of consent (4 patients) and prior chemotherapy, or multifocal tumor and unrecorded KPS (1 patient each). In addition, patients with tumors >40 mm at time of SRS (7 patients) were also excluded from the analysis. Patient characteristics are shown in Table 1 and were well balanced between the treatment groups.

Quality assurance compliance

Compliance with radiosurgery protocol guidelines was assessed in 79 (89%) evaluable patients and is shown in Table 2. Unacceptable deviations were scored in 14 patients (18%). Compliance with EBRT and BCNU guidelines was per protocol in most patients. Only 1.5% and 3.5% had unacceptable deviations from EBRT and BCNU, respectively.

Survival

At a median follow-up time of 61 months, 80 patients in arm 1 and 85 in arm 2 have died. The median survival was 13.6 months (95% CI, 11.0–14.8) in arm 1 and 13.5 months (95% CI, 11.2–15.2) in arm 2 ($p = 0.5711$). The 2- and 3-year survival rates for arm 1 were 19% and 13%, respectively, whereas for arm 2, they were 21% and 9%, respectively (Fig 1). These differences were not statistically significant. Similarly, a statistically significant difference between treatment arms was found neither in the subset of RTOG recursive partitioning analysis (RPA) class III and IV (11) patients (Fig. 2a) nor in the subset of patients with preoperative tumor size ≤40 mm (Fig. 2b). Furthermore, a comparison of SRS treatment techniques within arm 2 patients resulted in no survival difference (Fig. 2c). An intention-to-treat analysis including all randomized patients produced nearly identical results.

Patterns of failure

There was no significant difference between the two arms in the patterns of failure (Table 3). Local failure was a component of failure in 92.5% of all patients.

Quality of life

The pretreatment QOL questionnaire was completed by 88% of the patients; 70% of these completed the end-of-treatment QOL questionnaire. The primary reasons for noncompliance were that institutions either forgot to give the questionnaire to the patient or they completed the pretreatment questionnaire after the start of therapy. Table 3 indicates that 42% of arm 1 patients deteriorated from baseline at the end of treatment compared with 49% in arm 2 ($p = 0.699$). Using the MMSE only, approximately 25% of the patients had a cognitive decline during that time frame (Table 4). At the 3-month follow-up, one third of patients

Table 1. Pretreatment characteristics*

	Radiation therapy (n = 97)	Stereotactic radiosurgery + radiation therapy (n = 89)
Age		
18–39	8 (8%)	10 (11%)
40–49	23 (24%)	17 (19%)
50–64	45 (46%)	34 (38%)
65+	21 (22%)	28 (31%)
Mean	55.5	56.4
Range	28–79	18–79
Karnofsky performance score		
60	6 (6%)	4 (4%)
70	5 (5%)	14 (16%)
80	18 (19%)	11 (12%)
90	54 (56%)	40 (45%)
100	14 (14%)	20 (22%)
Gender		
Male	55 (57%)	56 (63%)
Female	42 (43%)	33 (37%)
Race		
White	96 (99%)	84 (94%)
Hispanic	1 (1%)	2 (2%)
Black	0	3 (3%)
Neurologic function		
No symptoms	23 (24%)	26 (29%)
Minor	53 (55%)	41 (46%)
Moderate/active	10 (10%)	13 (15%)
Moderate/<active	11 (11%)	9 (10%)
Mini-Mental Status Exam		
Missing	15	9
<24	7 (9%)	4 (5%)
≥24	75 (91%)	76 (95%)
Mean	27.1	28.1
Range	5–30	20–30
Preoperative tumor size (cm)		
n	96	86
Mean	4.0	3.9
Median	4.0	4.0
Range	1.4–9.0	1.5–7.5
Postoperative tumor size (cm)		
n	88	80
Mean	3.0	3.0
Median	3.0	3.0
Range	0.5–7.0	0.7–6.0
Recursive partitioning analysis class		
III	22 (23%)	19 (21%)
IV	48 (49%)	50 (56%)
V	24 (25%)	17 (19%)
VI	3 (3%)	3 (3%)
Spitzer Quality of Life Index		
n	85	79
Mean	7.8	7.6
Median	8	8
Range	2–10	3–10
Education level		
Grade 1–8	5 (6%)	6 (8%)
Some high school	10 (12%)	3 (4%)
High school/GED	28 (33%)	22 (29%)
College	42 (49%)	46 (60%)
Prefers not to answer	2	4
Unknown	10	8

* Percentages may not add up to 100% because of rounding.

Table 2. Stereotactic radiosurgery quality control

Evaluation	SRS + RT (*n* = 79)
Per protocol	40 (51%)
Variation acceptable	17 (22%)
Deviation unacceptable	14* (18%)
Dose	9
MDPD	4
Target coverage	1
PITV	3
Not evaluable	3 (4%)
Not applicable	5 (6%)

Abbreviations: SRS + RT = stereotactic radiosurgery + radiation therapy; MDPD = maximum dose divided by the prescription dose; PITV = prescription isodose surface volume divided by the target volume.

* Two patients had more than 1 major deviation.

experienced QOL deterioration compared with baseline. The MMSE indicated that 25% of the SRS patients had deteriorated by 3 months compared with 35% of arm 1 ($p = 0.21$). At 3 months, 33% of the patients in arm 1 had tumor progression compared with 22% in arm 2. This was correlated with QOL, with 52% of the progressing patients experiencing QOL deterioration compared with 34% of nonprogressing patients with QOL decline ($p = 0.035$). There was a similar trend in MMSE. At 1-year follow-up, QOL data were available for only 45% of live patients. The trends in terms of QOL decline are similar to the 3-month data, but the relatively small patient numbers make the results inconclusive. A quality-adjusted survival analysis showed no significant difference between the two arms.

Toxicity

Toxicities were graded using the acute and late morbidity scoring scheme recommended by the RTOG and the European Organization for Research in the Treatment of Cancer. Table 5 shows late radiation-related toxicities for arms 1 and 2. There were four Grade 3 late toxicities in the SRS arm, all in patients who received a 15-Gy SRS boost. Of the 59 patients who underwent surgery as salvage therapy, 3 (3/31) in arm 1 had documented necrosis only in the operative specimen and all others had active tumor. In the SRS arm, 7 patients (7/28) had necrosis only and the remaining had active tumor.

Grades 3–5 BCNU-related toxicity rates were 33.7%, 20.5%, and 2.4%, respectively, for the SRS arm and 33.7%, 21.0%, and 5.3%, respectively, for arm 1. The BCNU toxicities were not significantly different between the treatment arms.

Salvage therapy

Table 6 shows the salvage treatments used at the time of failure. Surgery was used at similar rates in both groups. Salvage chemotherapy was also similarly distributed between the two groups. As expected, SRS was more fre-

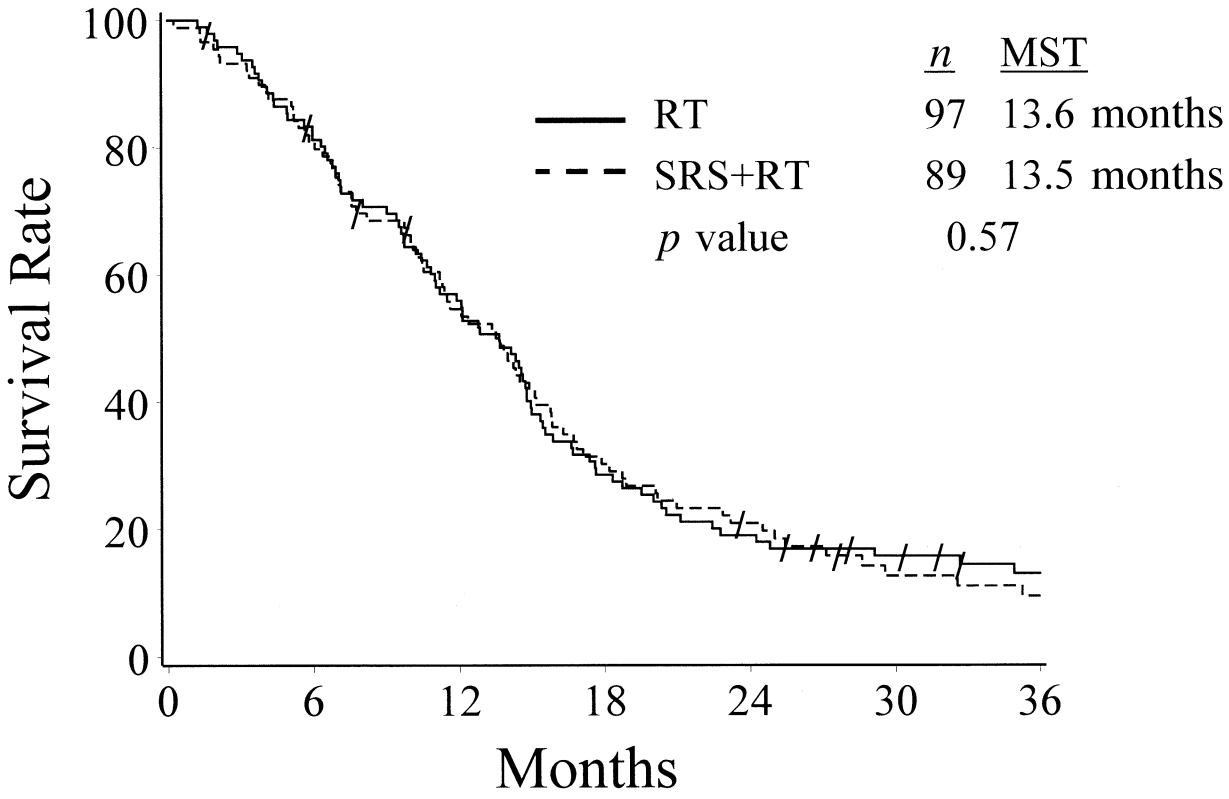


Fig. 1. Survival by treatment arm. RT = radiation therapy; SRS = stereotactic radiosurgery; MST = median survival time.

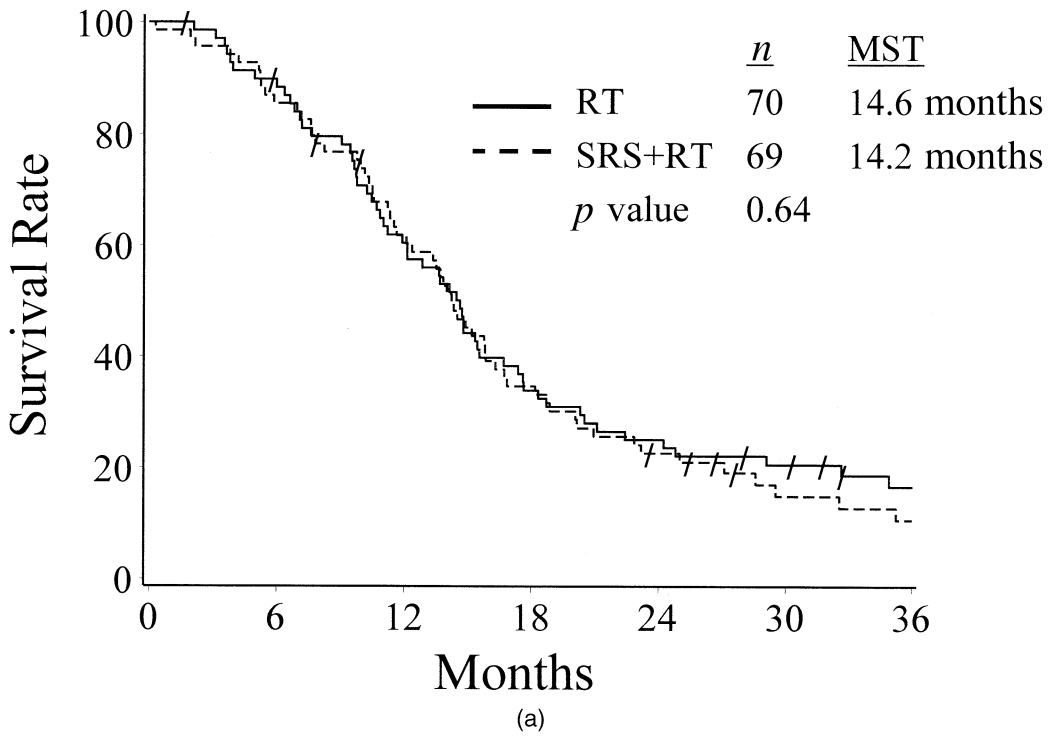
quently used as salvage therapy in the group receiving conventional radiation therapy alone as initial therapy.

DISCUSSION

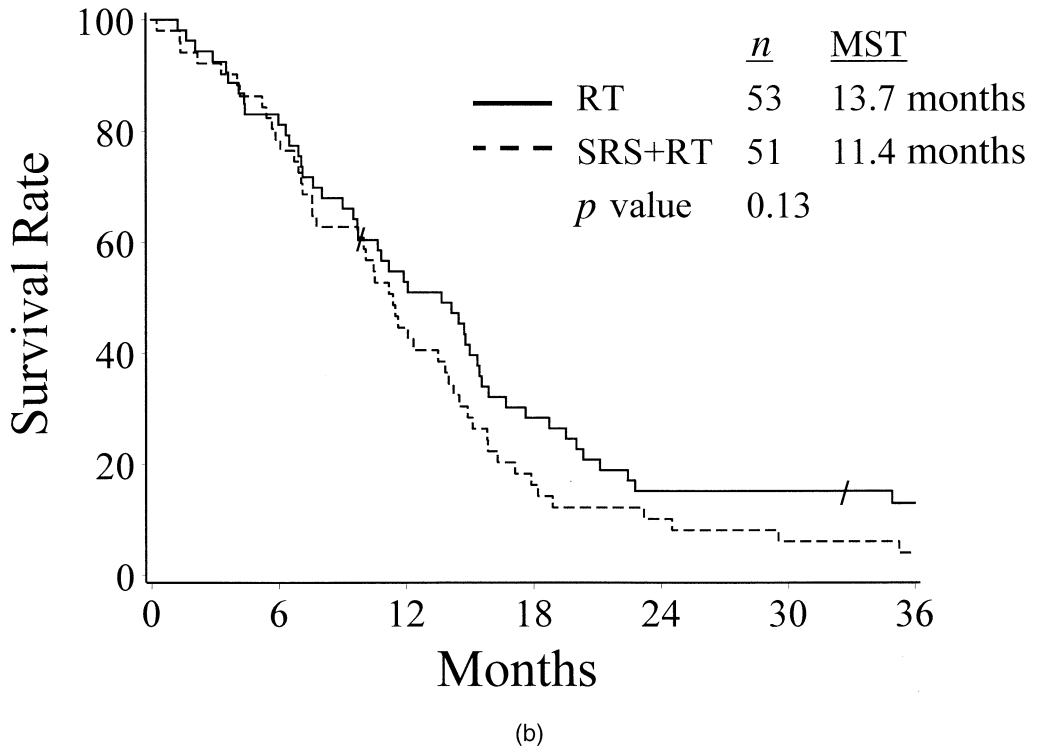
The poor results seen in the management of patients with GBM have led to the continuing search for novel therapeutic approaches. Despite maximal surgical resection and postoperative EBRT, most patients succumb to their disease, usually as a result of local tumor persistence or recurrence. A dose–response relationship has been shown in earlier studies of postoperative radiation therapy. Walker *et al.* (1), in a retrospective review of a series of sequential trials, reported an increase in median survival time from 28 to 42 weeks when the dose delivered increased from 50 to 60 Gy. A randomized trial by the Medical Research Council (2) confirmed an improvement in median survival from 9 to 12 months when 60 Gy was compared with 45 Gy. In a disease for which distant spread is a rare event and in which the majority of patients fail within 2 cm of the original tumor volume (3), escalating the total radiation dose focally became an attractive option for selected patients. The dose escalation in this trial was achieved by using stereotactic radiation techniques.

The use of a SRS boost in the initial management of patients with GBM has been explored for the past 15 years. Improved median survivals from SRS institutional reports (5, 6), coupled with promising survival benefit seen initially in patients treated with stereotactic brachytherapy (15), led to an increasing interest in the use of focal stereotactic boost. Sarkaria *et al.* (6) retrospectively studied 115 patients treated at three institutions and reported a significant improvement in both median and 2-year survival in favor of the SRS-treated patients. This improvement in survival was significant even when patients were stratified by the RTOG RPA prognostic classes and compared to historic controls from the RTOG database. However, in a disease in which the overall and median survival times are very limited, such improvement may have been a consequence of selection bias rather than a genuine treatment effect.

Although the RTOG RPA classes incorporate well-known prognostic factors, they do not include all prognostic variables, most notably the tumor size. Irish *et al.* (7) conducted a retrospective review of patients with malignant gliomas, treated with the EBRT, and analyzed the impact of case selection on survival. At completion of EBRT, 27% of patients were deemed potentially eligible for stereotactic radiosurgery (although they were not actually treated with radiosurgery) and a survival benefit was seen in this group. The median survival of these patients was 23.4 months compared with 8.6 months for the radiosurgery ineligible patients. Curran *et al.* (8), in a similar retrospective analysis from the RTOG database, also showed improved survival



(a)

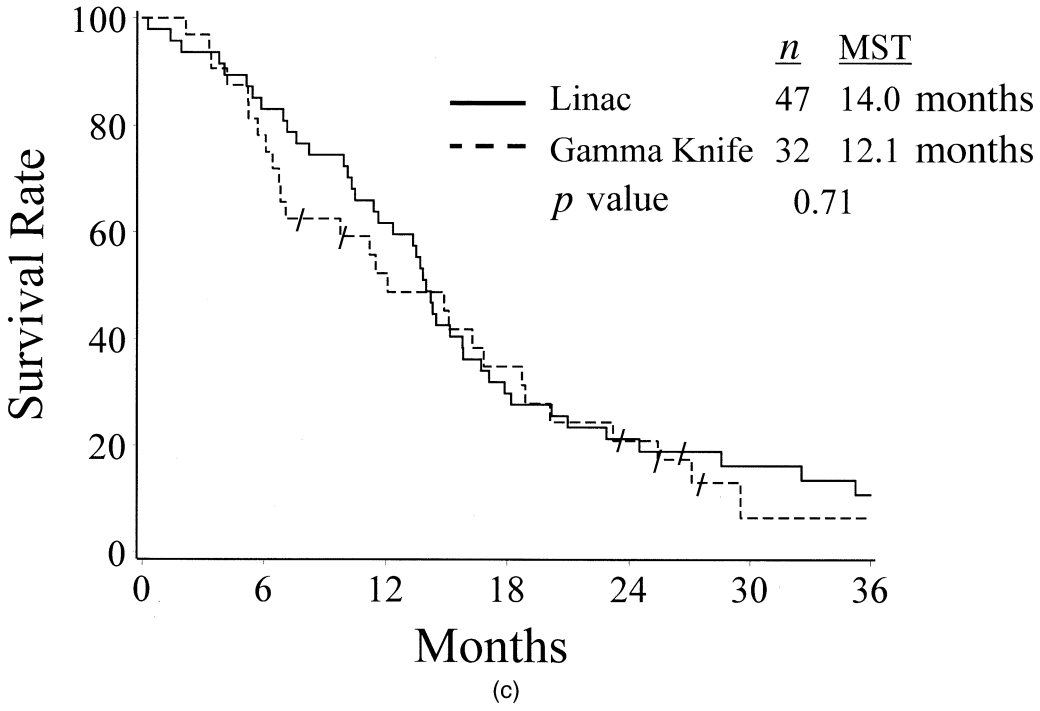


(b)

Fig. 2. (a) Survival by treatment: recursive partitioning analysis class III and IV. (b) Survival by treatment: preoperative tumor size ≤4 cm. (c) Survival by stereotactic radiosurgery (SRS) technique: arm 2, SRS + radiation therapy (RT). MST = median survival time.

for radiosurgery-eligible patients as compared with ineligible patients.

Our study was carried out to determine whether or not SRS boost followed by EBRT plus BCNU could improve the survival in patients with GBM. In contrast to previously reported Phase II studies, our large, multicenter, randomized trial did not demonstrate an improvement in survival for the SRS-treated patients. Even when subgroup analyses were performed, we could not identify any specific group that benefited from the addition of SRS. These results are



(c)

Fig. 2. (*Cont'd*).

Table 3. Patterns of failure

	Radiation therapy (n = 96)	Stereotactic radiosurgery + radiation therapy (n = 89)
Local only	51 (67%)	42 (58%)
Adjacent only	4 (5%)	2 (3%)
Local + adjacent	16 (21%)	18 (25%)
Nonadjacent only	0	1 (1%)
Local + nonadjacent	2 (3%)	1 (1%)
Local + adjacent + nonadjacent	3 (4%)	5 (7%)
Unknown	0	4 (5%)
No failure	20	16

Table 4. End of RT measures

End of RT	RT	SRS + RT
Spitzer Quality of Life Index		
n	62	49
Decline	26 (42%)	24 (49%)
Stable	15 (24%)	9 (18%)
Improve	21 (34%)	16 (33%)
p value	0.699	
Mini-Mental Status Exam		
n	59	49
Decline	19 (32%)	14 (29%)
Stable	19 (32%)	14 (29%)
Improve	21 (36%)	21 (43%)
p value	0.706	

Abbreviations: RT = radiation therapy; SRS = stereotactic radiosurgery.

Table 5. Late toxicities

	Radiation therapy (n = 87) Grade			Stereotactic radiosurgery + radiation therapy (n = 80) Grade		
	1	2	3	1	2	3
Ototoxicity	2	0	0	1	1	0
Skin	10	5	0	14	4	0
Neurologic	7	1	0	3	6	3
Other	13	5	1	10	7	1
Maximum toxicity reported per patient	17	6	0	10	9	4

Table 6. Salvage therapy*

	RT (n = 96)	SRS+RT (n = 89)
Surgery	34 (35%)	29 (33%)
Partial resection	16	14
Total resection	15	14
Shunt + total	1	1
Other type	5	7
Unknown type	3	0
Non-protocol RT	6 (6%)	6 (7%)
Non-protocol RS	18 (19%)	5 (6%)
Non-protocol chemotherapy	54 (56%)	47 (53%)

Abbreviations: RT = radiation therapy; SRS = stereotactic radiosurgery; RS = radiosurgery.

* These categories are not mutually exclusive. Some patients received more than 1 salvage therapy.

not completely surprising, because GBMs are inherently infiltrating neoplasms. Biopsy (16) and magnetic resonance spectroscopy (17) analyses have demonstrated significant microscopic tumor extension beyond the contrast-enhancing lesion, thereby limiting the effectiveness of focal radiotherapy.

Attempts to increase local control and, ultimately, survival by focally increasing the dose of irradiation also have met with little or no success in two randomized trials of stereotactic brachytherapy, another form of focal irradiation. Laperriere *et al.* (18) and Selker *et al.* (19) conducted Phase III studies in patients with malignant gliomas. These trials randomized patients to postoperative EBRT vs. the same EBRT plus a temporary stereotactic iodine-125 interstitial implant. In both studies, a survival benefit was not demonstrated for the group receiving brachytherapy.

Our current study also failed to demonstrate a change in the pattern of failure, with more than 90% of patients presenting a component of local failure. Furthermore, quality of life deterioration at the end of therapy was similar between the two arms and there was no difference in quality-adjusted survival between the two groups of patients.

In summary, our results demonstrate that SRS boost, as used in this trial, followed by EBRT and BCNU chemotherapy does not lead to improved survival and does not change the pattern of failure in selected patients with supratentorial GBM. Earlier reports indicating an improved survival for SRS-treated patients most likely reflect a selection bias rather than a beneficial effect of SRS. In this context, it is important to note that in many of those earlier reports SRS was employed at completion of EBRT rather than upfront. This temporal sequencing could potentially select out patients who improve or remain stable at completion of EBRT and whether SRS boost improves the survival of these patients cannot be answered by our trial.

REFERENCES

1. Walker MD, Strike TA, Sheline GE. An analysis of dose-effect relationship in the radiotherapy of malignant gliomas. *Int J Radiat Oncol Biol Phys* 1979;5:1725–1731.
2. Bleehen NM, Stenning SP. A Medical Research Council trial of two radiotherapy doses in the treatment of grades 3 and 4 astrocytoma. The Medical Research Council Brain Tumour Working Party. *Br J Cancer* 1991;64:769–774.
3. Hochberg FH, Pruitt A. Assumptions in the radiotherapy of glioblastoma. *Neurology* 1980;30:907–911.
4. Erlich SS, Davis RL. Spinal subarachnoid metastasis from primary intracranial glioblastoma multiforme. *Cancer* 1978; 42:2854–2864.
5. Loeffler JS, Alexander E, 3rd, Shea WM, *et al.* Radiosurgery as part of the initial management of patients with malignant gliomas. *J Clin Oncol* 1992;10:1379–1385.
6. Sarkaria JN, Mehta MP, Loeffler JS, *et al.* Radiosurgery in the initial management of malignant gliomas: survival comparison with the RTOG recursive partitioning analysis. *Int J Radiat Oncol Biol Phys* 1995;32:931–941.
7. Irish WD, MacDonald DR, Cairncross JG. Measuring bias in uncontrolled brain tumor trials—to randomize or not to randomize? *Can J Neurol Sci* 1997;24:307–312.
8. Curran WJ, Scott CB, Weinstein AS, *et al.* Survival comparison of radiosurgery-eligible and -ineligible malignant glioma patients treated with hyperfractionated radiation therapy and carmustine: A report of Radiation Therapy Oncology Group 83-02. *J Clin Oncol* 1993;11:857–862.
9. Shaw E, Kline R, Gillin M, *et al.* Radiation Therapy Oncology Group: Radiosurgery quality assurance guidelines. *Int J Radiat Oncol Biol Phys* 1993;27:1231–1239.
10. Shaw E, Scott C, Souhami L, *et al.* Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: Final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys* 2000;47:291–298.
11. Curran WJ, Scott CB, Horton J, *et al.* Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. *J Natl Cancer Inst* 1993;85:704–710.
12. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
13. Caplan RJ, Pajak TF, Cox JD. Analysis of the probability and risk of cause-specific failure. *Int J Radiat Oncol Biol Phys* 1994;29:1183–1186.
14. Kanji G. 100 statistical tests. London: Sage Publications; 1999.
15. Gutin PH, Prados MD, Phillips TL, *et al.* External radiation followed by an interstitial high activity iodine-125 implant boost in the initial treatment of malignant gliomas: NCOG study 6G-82-2. *Int J Rad Oncol Biol Phys* 1991;21:601–606.
16. Kelly PJ, Daumas-Duport C, Kispert DB, *et al.* Imaging-based stereotaxic serial biopsies in untreated intracranial glial neoplasms. *J Neurosurgery* 1987;66:865–874.
17. Castillo M, Smith JK, Kwock L, Wilber K. Apparent diffusion coefficients in the evaluation of high-grade cerebral gliomas. *Am J Neuroradiol* 2001;22:60–64.
18. Laperriere NJ, Leung PMK, McKenzie S, *et al.* Randomized study of brachytherapy in the initial management of patients with malignant astrocytoma. *Int J Radiat Oncol Biol Phys* 1998;41:1005–1011.
19. Selker RG, Shapiro WR, Burger P, *et al.* The Brain Tumor Cooperative Group NIH trial 87-01: A randomized comparison of surgery, external radiotherapy, and carmustine versus surgery, interstitial radiotherapy boost, external radiation therapy, and carmustine. *Neurosurgery* 2002;51:343–355.