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Phase II Trial of Radiosurgery to Magnetic Resonance Spectroscopy–Defined High-Risk Tumor Volumes in Patients With Glioblastoma Multiforme

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Abstract

Purpose—To determine the efficacy of a Gamma Knife stereotactic radiosurgery (SRS) boost to areas of high risk determined by magnetic resonance spectroscopy (MRS) functional imaging in addition to standard radiotherapy for patients with glioblastoma (GBM).

Methods and Materials—Thirty-five patients in this prospective Phase II trial underwent surgical resection or biopsy for a GBM followed by SRS directed toward areas of MRS-determined high biological activity within 2 cm of the postoperative enhancing surgical bed. The MRS regions were determined by identifying those voxels within the postoperative T2 magnetic resonance imaging volume that contained an elevated choline/*N*-acetylaspartate ratio in excess of 2:1. These voxels were marked, digitally fused with the SRS planning magnetic resonance image, targeted with an 8-mm isocenter per voxel, and treated using Radiation Therapy Oncology Group

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SRS dose guidelines. All patients then received conformal radiotherapy to a total dose of 60 Gy in 2-Gy daily fractions. The primary endpoint was overall survival.

Results—The median survival for the entire cohort was 15.8 months. With 75% of recursive partitioning analysis (RPA) Class 3 patients still alive 18 months after treatment, the median survival for RPA Class 3 has not yet been reached. The median survivals for RPA Class 4, 5, and 6 patients were 18.7, 12.5, and 3.9 months, respectively, compared with Radiation Therapy Oncology Group radiotherapy-alone historical control survivals of 11.1, 8.9, and 4.6 months. For the 16 of 35 patients who received concurrent temozolomide in addition to protocol radiotherapeutic treatment, the median survival was 20.8 months, compared with European Organization for Research and Treatment of Cancer historical controls of 14.6 months using radiotherapy and temozolomide. Grade 3/4 toxicities possibly attributable to treatment were 11%.

Conclusions—This represents the first prospective trial using selective MRS-targeted functional SRS combined with radiotherapy for patients with GBM. This treatment is feasible, with acceptable toxicity and patient survivals higher than in historical controls. This study can form the basis for a multicenter, randomized trial.

Keywords

Radiosurgery; Glioblastoma; Gamma Knife; Magnetic resonance spectroscopy; Functional imaging; Prospective Phase II

Introduction

Glioblastoma multiforme (GBM), or World Health Organization grade 4 glioma, is the most common adult primary brain tumor, with more than 12,000 cases diagnosed annually by American Cancer Society estimates (1). In randomized trials of patients with GBM, after maximal safe surgical resection, radiotherapy to doses of 60 Gy in conventional 1.8–2 Gy/d fractionation, as well as addition of chemotherapy to select younger patients, has been shown to improve survival (2, 3). Unfortunately, despite multimodality treatment, patients diagnosed with GBM have a poor prognosis, with median survivals averaging less than 1 year for most patients (4). Clearly, current therapy is suboptimal.

Stereotactic radiosurgery (SRS), which allows the delivery of very-high-dose, precise radiotherapy, has increased control and survival of patients with high-grade gliomas in retrospective and Phase II trials. A multi-institutional retrospective analysis of patients with high-grade gliomas reported that those patients receiving SRS in addition to surgery and conventional radiotherapy had a significantly improved 2-year and median survival compared with historical controls of patients treated without SRS (5, 6). In a study of 37 patients with high-grade gliomas <4 cm, treatment with SRS in addition to conventional radiotherapy resulted in 75% of patients being alive and stable at a median follow-up of 19 months (7). Results of another Phase II study of patients with high-grade gliomas receiving three weekly concomitant boosts in addition to lower-dose conventional radiotherapy showed median survivals of 33 months for anaplastic astrocytomas and 16 months for GBM, which were higher than for historical non-SRS controls (8, 9).

Because retrospective and Phase II data determined that an SRS boost in addition to conventional radiotherapy for patients with high-grade gliomas was feasible and probably efficacious, a national Phase III trial was undertaken by the Radiation Therapy Oncology Group (RTOG 93-05), in which patients with small (<4 cm) supratentorial GBM were randomized to conventional radiotherapy with or without a stereotactic radiosurgical boost to the contrast-enhancing postoperative surgical bed (10). Although this trial failed to demonstrate a survival advantage by boosting the contrast-enhancing surgical bed, an American Society for Radiation Oncology (ASTRO) review statement regarding the use of SRS in the treatment of malignant gliomas (11) stated, “[The] optimal SRS boost therapy remains to be elucidated. One possible flaw with SRS boost techniques is the use of targeting the visible contrast enhancing lesion. Magnetic resonance spectroscopy (MRS) studies have documented areas of increased metabolic activity outside the region of contrast enhancement. This leaves the possibility that better SRS boost techniques and better patient selection may improve survival as compared with conventionally treated patients who are treated without a SRS boost.”

Efforts have been directed toward accurately defining high-risk regions of high-grade gliomas that appear more aggressive and may benefit from additional targeted limited-volume SRS without the increased risk of large-volume treatment toxicity. Magnetic resonance spectroscopy (MRS), positron emission tomography imaging using radiolabeled glucose as well as methionine, and MR tumor perfusion imaging are noninvasive functional imaging techniques that are being used in addition to conventional MR imaging (MRI) to help identify high-risk regions in large gliomas (12–15). Of these techniques, MRS has the broadest availability and reported experience. It has been shown that in MR spectra, active gliomas exhibit a high resonance in the choline spectral peak and a low NAA (*N*-acetylaspartate) or creatine resonance correlating with high choline/NAA or choline/creatine ratios for active tumors vs. low ratios for areas of inactivity (16). In an analysis of 36 patients with recurrent high-grade gliomas treated with SRS, patients with MR spectroscopic high-risk regions that were within the SRS target had an improved survival and increase in time to further treatment compared with those patients with MR spectroscopic high-risk regions outside the SRS target (15). In a study of 31 patients with high-grade gliomas resected after conventional MRI and MRS, MRS was found to more accurately define the tumor boundary than conventional MR using histopathologic correlation (17). On pretreatment analysis of 34 patients with high-grade gliomas, high-risk regions by MRS were found to be significantly smaller than in conventional T2 imaging, suggesting an ability to decrease the amount of normal brain tissue within the MRS-determined target, thus potentially limiting side effects (13).

The purpose of this prospective Phase II study was to determine the feasibility and efficacy of a stereotactic radiosurgical boost directed at high-risk tumor regions as determined by MRS combined with standard conformal radiotherapy for patients with GBM.

Methods and Materials

Patient selection

Between December 2002 and September 2007, 35 patients with newly diagnosed GBM were enrolled in this prospective Phase II trial, which was registered with www.clinicaltrials.gov (ID no. NCT00253448) and was approved by the University Hospitals of Cleveland institutional review board. All patients signed detailed informed consent forms approved by the institutional review board. The protocol was annually reviewed by the University Hospitals of Cleveland data safety monitoring committee. All patients underwent either biopsy or surgical resection to confirm the diagnosis of GBM and were reviewed at a multidisciplinary neuro-oncology tumor board with confirmation by a neuropathologist at University Hospitals (M.C.). Inclusion and exclusion criteria are listed in Table 1.

MRS and pretreatment MRS image processing

All patients underwent postoperative MRS with a $10 \times 10 \times 15$ -mm voxel size. The entire area of T2 abnormality on each postoperative scan was analyzed. Choline, NAA, and creatine spectrographic peaks were identified, with choline and NAA normalized to baseline creatine levels. If creatine levels were 0, no data were identified for that voxel. Those voxels with a normalized choline/NAA ratio in excess of 2 were manually identified and marked. Those marked voxels were highlighted on the T2 sequence, and another DICOM (Digital Imaging and Communications in Medicine) image set (MARKED-MRS) with the highlighted voxels was created using the image fusion and voxel paint routines on MIM-Vista Software (Cleveland, Ohio) versions 3.0 to 3.5. The MARKED-MRS DICOM image set was then transferred to the Gamma Knife treatment-planning console.

Gamma Knife SRS

All patients underwent Gamma Knife SRS within 5 weeks of surgery, with use of either a Model B or 4C Leksell Gamma Knife unit (Elekta, Stockholm, Sweden) with ^{60}Co sources. During treatment planning the MARKED-MRS scan was fused with the Gamma Knife planning frame-based scan using the fusion function within the Gamma Plan Gamma Knife planning software. The highlighted voxels on the MARKED-MRS scan within 2 cm of the contrast-enhancing lesion on the Gamma Knife planning scan were targeted with a single 8-mm isocenter to the 50% isodose curve (Fig. 1). The combined isocenters from all treated highlighted voxels created the final treatment plan. The volume of the dose matrix within the 50% isodose curve was measured. An equivalent sphere diameter of that volume was created using $4/3\pi(\text{diameter}/2)^3$. On the basis of the RTOG 90-05 criteria (18), the prescription dose was 15 Gy for diameters 3–4 cm, 18 Gy for diameters 2–2.9 cm, and 24 Gy for diameters <2 cm. If the diameter was calculated to be >4 cm, the patient was not a candidate for the trial and was offered off-protocol treatment. All patients received a loading dose of an anticonvulsant 1 day before SRS and intravenous (i.v.) dexamethasone on the day of SRS. Stereotactic radiosurgery was performed before conformal radiotherapy to minimize impact of postradiation changes on the MRS analysis.

Conformal radiotherapy

All patients underwent three-dimensional conformal radiotherapy within 2 weeks of completing SRS. Intensity-modulated radiotherapy was not allowed, to achieve uniformity in the treatment plans and to minimize low-dose spill beyond the planning target volumes. One treatment of 2.0 Gy was given daily 5 days per week for a total of 60.0 Gy. All portals were treated during each treatment session. Each patient was treated in the supine position, with a thermoplastic mask used for reproducibility. All patients underwent postoperative MRI within 2 days of surgery. For the first 46 Gy in 23 fractions, the treatment volume included the volume of contrast-enhancing lesion and surrounding edema on postoperative MRI scan plus a 2-cm margin. If no surrounding edema was present, the initial target volume included the T1 contrast-enhancing lesion plus a 2.5-cm margin. After 46 Gy, the boost tumor volume included the T1 contrast-enhancing lesion (without edema) on the postoperative MRI scan plus a 2.5-cm margin and was treated with an additional 14 Gy in 7 fractions. The conformal radiotherapy treatment plans always included the area treated with SRS because the boosted voxels were within 2 cm of the contrast-enhancing lesion. Treatment plans included a wedge pair of fields, rotation, or multiple-field techniques. No straight opposed lateral fields were used. Doses were specified as the target dose that was the center of the target volume, and the minimum dose to the target volume was kept within 10% of the center of the volume. Critical structures and constraints included the lenses to 10 Gy, optic nerves to 50 Gy, optic chiasm to 60 Gy, cochlea to 55 Gy, brainstem to 60 Gy, and the spinal cord to 45 Gy.

Patient follow-up and statistical analysis

Follow-up consisted of an evaluation by a member of our multi-disciplinary brain tumor group and MRI at 1 month after completion of conformal radiotherapy and then every 3 months after treatment, or more often if indicated. All MR images were reviewed in our neuro-oncology tumor board. A computerized database was compiled using all available patient data. Overall survival was measured from the date of SRS treatment to the date of death and censored at the date of last follow-up for survivors. The survivor function was estimated by the Kaplan-Meier method (19), and the difference between/among groups was examined by log-rank test. Subsequent treatment for patients who recurred after completing this protocol treatment was at the discretion of treating physicians and included additional surgery, chemotherapy, or a second protocol. Multivariate analysis was not reported because this was determined by the statistician to be unreliable owing to the small sample size, which was chosen to detect overall survival differences and not subset differences. All tests are two-sided, and a p value of 0.05 was considered statistically significant.

Results

Patient characteristics

Patient characteristics are listed in Table 2. All RTOG RPA class patients with GBM (Classes 4–6) were included in the study. The mean age of patients was 62 years, the median Karnofsky performance status was 90, and the median RPA class was 5. The majority of patients underwent a subtotal resection before SRS. Approximately half of patients (46%) received concurrent temozolomide chemotherapy at the discretion of the neuro-oncologist.

Temozolomide was not given to the initial 54% of patients because the European Organization for Research and Treatment of Cancer (EORTC) Phase III data were not yet published at the time this trial was started.

Survival

The primary endpoint of this study was overall survival from the time of SRS. Overall survival was used as the primary endpoint of this trial because of controversy separating local progression from postradiation changes; hence, local control was not specifically analyzed. The median survival of the entire cohort was 15.8 months (95% confidence interval [CI] 11–19.9 months) (Fig. 2a). Univariate analysis identified age, initial surgery type, concurrent chemotherapy, and RTOG RPA class to be significant prognostic factors (Table 3). Patients older than 60 years had a median survival of 11 months, compared with 22 months for patients younger than 60 years ($p = 0.004$). Patients with a gross total resection or subtotal resection had a median survival of 17 months, compared with 6 months for those with a biopsy ($p = 0.004$). The median survival of RPA Class 3 patients is in excess of 22 months and has not yet been reached because 3 of 4 patients in this group are still alive. The median survivals for Class 4, 5, and 6 were 18.7 months (95% CI 14.5–29.1 months), 12.5 months (95% CI 9.2–18.5 months), and 3.9 months (95% CI 2.7–5.1 months), respectively ($p < 0.0001$) (Fig. 2b). The median for those treated without concurrent chemotherapy was 11 months (95% CI 7.2–18.5 months) vs. 20.8 months (95% CI 14.2–29.1 months) for those treated with concurrent chemotherapy ($p = 0.037$) (Fig. 2c).

Comparison with historical controls

When compared with published data from RTOG trials of patients treated with radiotherapy alone for malignant gliomas, the median survivals of patients in our cohort for each RPA class were substantially higher than those reported from RTOG trials of patients with malignant gliomas treated with radiotherapy alone (20) (Table 4). The median survival of patients in our cohort compared with RTOG was >22 vs. 17.9 months for Class 3; 18.7 vs. 11.1 months for Class 4; and 12.9 vs. 8.9 months for Class 5. When compared with patients receiving conventional radiotherapy and concurrent temozolomide chemotherapy on the EORTC trial, the results also favored treatment with MRS-targeted SRS, with median patient survival of our cohort compared with EORTC chemo/radiotherapy trial data (21) of >22 vs. 21.4 months for Class 3; 18.7 vs. 16.3 months for Class 4; and 12.9 vs. 10.3 months for Class 5. The RPA class breakdown of the 16 patients who received concurrent temozolomide was RPA Class 3 (4 patients), Class 4 (7 patients), and Class 5 (4 patients). The overall median survival of the patients who received concurrent temozolomide was 20.8 months vs. 14.6 months for the EORTC chemo/radiotherapy patients, showing a substantial difference of 6.2 months (Table 4).

Treatment toxicity

Grade 3 or 4 toxicity was reported in 9 of the 35 patients (26%). These included a stroke 2 days after SRS in a single patient taking warfarin. The remaining 8 patients required reoperation for neurologic symptoms associated with radiographic changes. Five of the 8 patients were found to have recurrent tumor, and 3 of the 8 patients had symptomatic

radiation necrosis. All of the radiation necrosis was within the SRS volume. Therefore the number of patients with grade 3 or 4 toxicity possibly attributable to treatment was 4 out of 35 (11%).

Discussion

This study is the first published prospective Phase II trial using MRS-targeted SRS in the treatment of patients with GBM. Standard treatment options and projected survivals for patients with newly diagnosed GBM remain dismal. Median survival with radiotherapy alone is approximately 12.1 months, increasing to 14.6 months with the addition of concurrent temozolomide, as demonstrated in the EORTC study (21). This 2.5-month increase in median survival resulted in a change in the standard of care to incorporate concurrent temozolomide with radiotherapy. The median survival of our entire cohort using MRS-targeted SRS was 15.6 months, increasing to 20.8 months for those patients receiving MRS-targeted SRS and concurrent temozolomide. This is a substantial increase over expected survival compared with historical controls (4, 21).

Potential pitfalls of our study include the potential selection biases of a Phase II trial. These were minimized by including poor-performing patients (RPA Class 6) and offering concurrent chemotherapy after the results of the EORTC randomized trial were reported. The cohort who received concurrent temozolomide showed median survivals 6.2 months higher than expected from the EORTC historical results alone (20.8 months vs. 14.6 months), indicating a further benefit of MRS-targeted SRS in addition to concurrent temozolomide and conventional radiotherapy.

Another potential criticism of the trial is the use of radio-surgical boost in light of the negative RTOG 93-05 results. We believe that the use of a functional boost as determined by MRS is more selective and possibly more specific for tumor rather than postsurgical changes potentially resulting in increased efficacy compared with boosting the contrast enhancement exclusively. Although the MRS-targeted SRS boost was delivered via Gamma Knife in this study, it is quite possible that other devices can be used to deliver the same single-fraction treatment, as long as fusion of the MRS scan is possible with the individual device treatment-planning software. This functional boost volume is also potentially smaller than the contrast-enhancing lesion, making some patients candidates for this type of boost who may not have been candidates for RTOG 93-05. Finally, the ASTRO review consensus statement (11) specifically stated that the use of more selective radiosurgical boosts as determined by functional imaging such as MRS was promising and should be pursued despite the RTOG 93-05 results. Our study was initiated before the completion of RTOG 93-05 and continued on the basis of the positive recommendation of the ASTRO consensus statement for MRS-targeted radiosurgical boosts.

At the time of initiation of our trial in 2002, MRS was only available at major academic medical centers. Since then, MRS has been more widely integrated into many large and small cancer centers. Although single-fraction SRS was used, it is also possible that a multifraction SRS boost could be delivered with MRS targeting. However, the radiobiology of a multifraction approach may not yield the same results. At this point there are enough

centers with MRS availability that, given the positive results of our trial, a multicenter Phase III or randomized Phase II trial incorporating a functional MRS-targeted radiosurgical boost for GBM is now feasible.

Conclusions

We report the first prospective Phase II trial of MRS-targeted SRS directed only to areas of high biologic activity combined with conformal brain radiotherapy for patients with GBM. Our findings show that this treatment is feasible with acceptable toxicity. The overall survival of patients treated with MRS-targeted SRS is higher than historical controls of patients treated with conformal radiotherapy alone as well as conformal radiotherapy combined with temozolomide. With the more widespread availability of MRS, this study can now form the basis for a multicenter randomized trial using an MRS-targeted “selective functional boost,” as supported by the ASTRO consensus report.

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Summary

This represents the first prospective Phase II trial using selective magnetic resonance spectroscopy (MRS)-targeted functional SRS stereotactic radiosurgery combined with radiotherapy for patients with glioblastoma (GBM). The study demonstrates that MRS-targeted SRS treatment is feasible, with acceptable toxicity and patient survivals higher than historical controls.

Fig. 1. Magnetic resonance (MR) spectroscopy Gamma Knife stereotactic radiosurgery procedure. NAA = *N*-acetylaspartate; RTOG = Radiation Therapy Oncology Group.

Fig. 2. Overall survival. (a) Kaplan-Meier estimation of overall survival with 95% confidence interval. The median survival time was 15.8 months (95% confidence interval 11–19.9 months). (b) Kaplan-Meier estimation of overall survival by recursive partitioning analysis (RPA) class. (c) Kaplan-Meier estimation of overall survival by concurrent chemotherapy status.

Table 1**Patient inclusion, exclusion criteria, and treatment schema**

Inclusion criteria
Histopathologically confirmed WHO grade 4 malignant glioma (glioblastoma)
Diagnosis made by surgical biopsy or resection
Patient must have recovered from effects of surgery or any postoperative complication
Therapy must begin within 5 wk of surgery
A diagnostic contrast-enhanced MRI scan with MR spectroscopy must be performed postoperatively before initiation of radiotherapy, including radiosurgery
Area of high risk defined on postoperative MR spectroscopy must meet the following radiosurgery criteria: maximum diameter 40 mm, located >5 mm from the optic nerve or chiasm, and does not involve the brainstem
No previous in-field radiotherapy to the head-and-neck area
No chemotherapy in 6-wk period before study
Age 18 y
Life expectancy 3 mo
KPS 50
Able to give informed consent
Exclusion criteria
Patients whose postoperative MR spectroscopic high-risk regions do not meet radiosurgery criteria
Multifocal malignant glioma
Recurrent malignant glioma
Inability to obtain a histologic confirmation of glioblastoma
Pregnancy
Start of therapy more than 5 wk after surgery
Treatment schema: surgery (Day 0); MRS by Day 35; SRS by Day 35; conformal radiotherapy (30 treatments 5 d/wk) to start by Day 49

Abbreviations: WHO = World Health Organization; MRI = magnetic resonance imaging; KPS = Karnofsky performance status.

Table 2

Characteristics of 35 patients enrolled in CWRU 1302

Patients	35 (100)
Age (y)	
Median	62
Range	21–84
Gender	
Male	17 (49)
Female	18 (51)
KPS	
Median	90
Range	60–100
RPA class	
3	4 (11)
4	13 (37)
5	16 (46)
6	2 (6)
Concurrent chemotherapy	
Yes	16 (46)
No	19 (54)
Surgical resection	
Biopsy	4 (11)
Subtotal	27 (78)
Gross total	4 (11)

Abbreviations: CWRU = Case Western Reserve University; RPA = recursive partitioning analysis. Other abbreviation as in Table 1.

Values are number (percentage) unless otherwise noted.

Table 3

Kaplan-Meier estimation of overall survival (OS) by the levels of a factor

Factor	n	OS (%) at 6 mo	OS (%) at 12 mo	OS (%) at 18 mo	OS (%) at 24 mo	p
Concurrent chemotherapy						0.037
0 (No)	19	79	47.4	31.6	10.5	
1 (Yes)	16	93.8	81.3	61.4	26.9	
RPA class						<0.0001
3	4	100	100	75	—	
4	13	92.3	76.9	59.8	25.6	
5	16	87.5	50	31.3	7.8	
6	2	0	—	—	—	
Sex						0.684
Female	18	72.2	55.6	38.9	21.6	
Male	17	100	70.6	51.8	16.2	
Age (y)						0.004
60	15	93.3	86.7	65.5	43	
>60	20	80	45	30	0	
Initial surgery type						0.004
Biopsy	4	50	25	—	—	
Gross total resection	4	100	75	75	—	
Subtotal resection	27	88.9	66.7	47.1	21.8	
Re-resection						0.656
No	27	81.5	63	43.5	21.7	
Yes	8	100	62.5	50	—	

Abbreviation as in Table 1.

Table 4

Summary of patient survival time by prognostic classification

Classification	No. of patients	Survival time (mo)			
		GK MRS median survival	RTOG historical control, XRT alone	Survival difference of GK MRS patients vs. historical control	Survival difference of GK MRS patients vs. historical control
RTOG RPA Class 3	4	>22*	17.9	4.1 [†]	0.6 [†]
RTOG RPA Class 4	13	18.7	11.1	7.6 [†]	2.4 [†]
RTOG RPA Class 5	16	12.9	8.9	4.0 [†]	2.6 [†]
Concurrent temozolomide	16	20.8	NA	NA	6.2 [†]

Abbreviations: GK = Gamma Knife; MRS = magnetic resonance spectroscopy; RTOG = Radiation Therapy Oncology Group; XRT = radiotherapy; EORTC = European Organization for Research and Treatment of Cancer; NA = Not applicable. Other abbreviation as in Table 2.

* Median survival not yet reached at time of analysis.

[†] Statistically significant.