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ORIGINAL ARTICLE

Survival following stereotactic radiosurgery for newly diagnosed and recurrent glioblastoma multiforme: a multicenter experience

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Abstract Despite decades of clinical trials investigating new treatment modalities for glioblastoma multiforme (GBM), there have been no significant treatment advances since the 1980s. Reported median survival times for patients with GBM treated with current modalities generally range from 9 to 19 months. The purpose of the current study is to retrospectively review the ability of CyberKnife® (Accuray Incorporated, Sunnyvale, CA, USA) radiosurgery to provide local tumor control of newly diagnosed or recurrent GBM. Twenty patients (43.5 %) underwent CyberKnife treatment at the time of the initial diagnosis and/or during the first 3 months of their initial clinical management. Twenty-six patients (56.5%) were treated at the time of tumor recurrence or progression. CyberKnife was performed in addition to the traditional therapy. The median survival from diagnosis for the patients treated with CyberKnife as an initial clinical therapy was 11.5 months (range, 2–33) compared to 21 months (range, 8–96) for the patients treated at the time of tumor recurrence/progression. This difference was statistically significant (Kaplan–Meier analysis, $P=0.0004$). The median survival from the CyberKnife treatment was 9.5 months (range, 0.25–31 months) and 7 months (range, 1–34 months) for patients in the newly diagnosed and recurrent GBM groups (Kaplan–Meier analysis, $P=0.79$), respectively. Cox proportional hazards survival regression analysis demonstrated that survival time did not correlate significantly with treatment parameters (D_{max}, D_{min}, number of fractions) or target volume. Survival time and recursive partitioning analysis class were not correlated ($P=0.07$). Patients with more extensive surgical interventions survived longer ($P=0.008$), especially those who underwent total tumor resection vs. biopsy ($P=0.004$). There is no apparent survival advantage in using CyberKnife in initial management of glioblastoma patients, and it should be reserved for patients whose tumors recur or progress after conventional therapy.

Keywords Brain tumors · Cyberknife radiosurgery · Glioblastoma multiforme · Multicenter study · Stereotactic radiosurgery · Survival

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Introduction

Despite decades of research investigating new treatment modalities for glioblastoma multiforme (GBM), there have been no significant treatment advances reflected in outcome since the 1980s [12]. Conventional treatment programs, which include surgical resection, chemotherapy, external beam radiation therapy, brachytherapy, or some form of stereotactic radiosurgery (SRS), function as palliative measures. Reported median survival times for patients with GBM treated with combinations of these options generally range from 9 to 19 months [6, 8, 14, 18, 28, 30, 38, 41, 43]. Although the pathogenesis of GBM is complex and multiple factors may be responsible for the ultimate outcome of treatment [39], an increased emphasis on local tumor control has been recommended due to the fact that the majority of patients develop local recurrences, often within 2 cm of the initial tumor location [2, 17, 24, 44].

SRS has been explored as an option for treating GBM. Gamma Knife® (Elekta AB, Stockholm, Sweden) and linear accelerator (linac)-based systems are the two primary systems for delivering SRS without surgical implantation of radiation sources, e.g., brachytherapy. The Gamma Knife system uses Cobalt-60 1.25-MeV radiation sources, and linac-based systems typically use 6 MeV photons as the radiation type [23, 25, 42]. While the CyberKnife® Radiosurgery System (Accuray Incorporated, Sunnyvale, CA, USA) is also a linac-based system, far fewer studies exist on its efficacy for GBM, due to this system's relatively short history.

The CyberKnife System [1, 7] combines computer-controlled robotics with real-time image guidance to provide high conformality without resorting to aggressive fixation of the target, therefore offering an attractive option for hypofractionated treatment. Because it allows local dose escalation to surgically inaccessible or previously irradiated areas with high precision, it may constitute a useful alternative in treatment of GBM for select patients.

The appropriate timing and role of SRS in the treatment of GBM as an upfront treatment option has been investigated using Gamma Knife SRS delivery systems. These studies have suggested that Gamma Knife SRS is more appropriate as a treatment option for recurrent tumors than as an upfront radiosurgical boost [13, 18, 33, 41]. Therefore, we considered it important to retrospectively review the efficacy of CyberKnife radiosurgery in the treatment of newly diagnosed or recurrent glioblastoma multiforme, as the outcome of these patients who had undergone such treatment became available.

Methods

Patients

In order to compare the survival rate of patients treated with CyberKnife either as radiosurgical boost after initial treatment or at the time of tumor recurrence, we undertook a retrospective study to review the cases of 46 patients treated between August 2002 and September 2005. Patients were treated at the Rocky Mountain CyberKnife Center in Boulder, CO, the Department of Neurosurgery at Stanford University School of Medicine, and the Department of Neurosurgery at Besta Neurological Institute in Milan, Italy.

Patients with histopathologically verified diagnoses of GBM were apportioned into newly diagnosed or recurrent GBM patient groups. The former group included 20 (43.5%) patients that had had CyberKnife radiosurgery as primary treatment intent or radiosurgical boost shortly after surgery or surgery and standard fractionated radiotherapy (external beam radiation therapy, EBRT). The recurrent GBM group included 26 (56.5%) patients treated at the time of tumor recurrence or progression. Timing of radiosurgery treatment was determined based on patients' clinical status, personal preferences, or recommendations of the treating physicians. Tumors in any location and treatment volume less than 50 cm^3 were considered for treatment. The median time from the diagnosis to CyberKnife treatment was 3 months (range, 1–3 months) and 13 months (range, 5–89 months) for newly diagnosed and recurrent tumors, respectively. Demographic and clinical patient criteria are presented in Table 1. Overall, the only statistically significant differences between the newly diagnosed and recurrent GBM groups were the mean EBRT dose they had received, which was higher in the recurrent GBM group ($P=0.001$, t test) and the average recursive partitioning analysis (RPA) class [11], which was higher in the newly diagnosed GBM patient group and was statistically significant ($P=0.025$, t test).

There were 21 and 30 treated lesions, 11 (55%) and 15 (57.7%) gross-total resections, and five (25%) and nine (35%) subtotal resections as initial clinical management in the newly diagnosed and recurrent GBM patient groups, respectively. The rest of the patients had undergone stereotactic biopsy.

Cyberknife treatment

A nonisocentric, individualized treatment plan was generated using contrast-enhanced axial computed tomography (CT) images at 1.25 mm slice thickness, acquired along the length of the skull and upper neck, from which digitally reconstructed radiographs were derived to facilitate skull tracking for stereotactic treatment guidance. In addition, two separate acquisitions of postcontrast axial T_1-weighted magnetic resonance (MR) images and volumetric three-dimensional T_2-weighted images were three-dimensionally fused with the planning CT scan. These were then transferred to the CyberKnife workstation where the visually detectable treatment target volume (excluding edema) and its relations to surrounding critical structures were outlined. For the patients who did not have an

Table 1 Patient demographics

	Newly diagnosed	Recurrent	Total
Patients (*N*)	20	26	46
Male/female ratio	13/7	18/8	31/15
Average age[a]	61.3 (27–81)	56.4 (36–82)	58.5 (27–82)
Total resection	11 (55%)	15 (57.7%)	26 (56.5%)
EBRT	15 (75%)	26 (100%)	41 (89%)
EBRT dose (Gy)[a]	54 (40–60)	60 (50–63)	58 (40–63)
Chemotherapy	15 (75%)	25 (96%)	40 (87%)
Karnofsky score[a]	82 (60–100)	84 (50–100)	83 (50–100)
RPA class[a]	4.5 (3–6)	3.9 (3–6)	4.2 (3–6)

EBRT external beam radiotherapy, *RPA* recursive partitioning analysis

[a] Mean values are presented with ranges in parentheses

enhancing tumor at the time of stereotactic radiosurgery treatment, the surgical cavity was treated with at least a 5-mm margin. An inverse treatment planning method was used to limit the maximum radiation dose delivered to such critical structures as the optic chiasm or brainstem. The CyberKnife system's treatment planning process was previously described [10]. Treatment planning was carried out using artificial anatomical tuning structures to constrain the dose distribution and maintain tight conformality in the dose gradient around the enhancing lesion between the 60% to 10% isodose lines (Fig. 1a, b).

The radiation dose was prescribed to the 65–89% isodose contour as normalized to the maximum dose (median 76%; Table 2). Other radiosurgical treatment parameters are detailed and summarized in Table 2. There were no statistically significant differences in radiosurgical treatment parameters between the groups.

For treatment, the patient was placed in the treatment position wearing a custom-made immobilization mask. The system acquired orthogonal X-rays which were registered to the radiographs reconstructed from pretreatment CTs. Computations required to bring the images into alignment were communicated to the treatment table to adjust the patient's position to match the pose of the patient during simulation. Skull tracking was performed every five beams throughout treatment delivery to ensure maintenance of optimal position. Treatment was delivered by a linear accelerator mounted on a robotic arm. On average, more than 100 nonisocentric beams were used to irradiate a single target stereotactically, with exceptional homogeneity within the target volume [45]. Patients who were on prophylactic corticosteroid prescription prior to their treatment were kept on their medication, and those who were not were administered corticosteroids posttreatment to relieve or prevent potential edemas.

Clinical outcome evaluation

Clinical and neurological evaluations were performed every 3 months with imaging obtained to assess local tumor response (Fig. 2a, b). Information regarding patient outcomes was obtained from charts, or if this was not available, the referring oncologist was contacted to obtain the information or the time and cause of death.

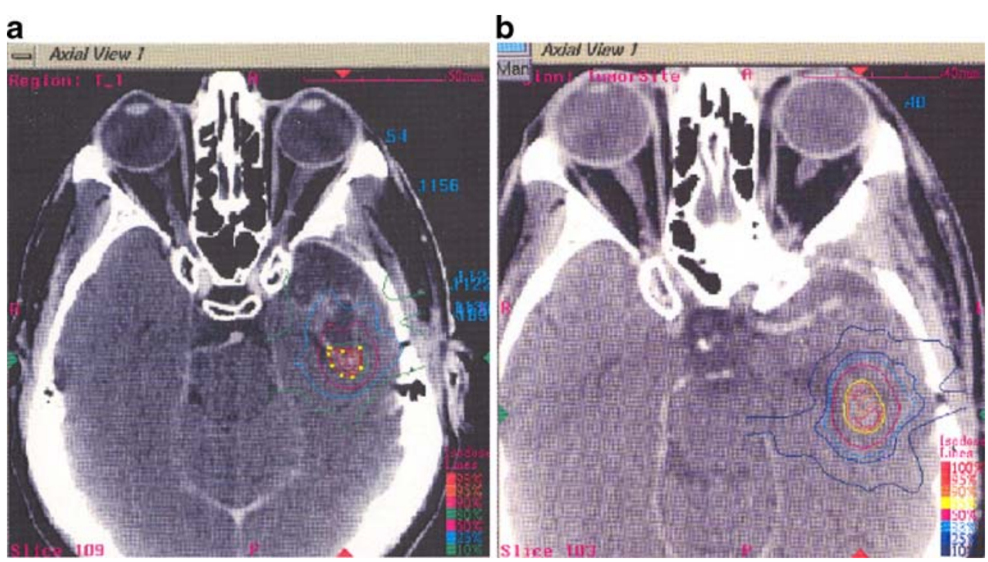

Fig. 1 **a** Treatment planning for GBM primary tumor. **b** Treatment planning for recurrent GBM

Table 2 Radiosurgical treatment parameters

	Newly Diagnosed	Recurrent	Overall
Target volume (cm^3)	5.8 (0.7–47.3)	7.0 (0.4–48.5)	7.0 (0.4–48.5)
Prescribed isodose (%)	74.9 (66.1–89.0)	77.7 (65.0–88.0)	76.0 (65.0–89.0)
Dmax (Gy)	27.6 (16.9–36.9)	25.8 (11.4–36.8)	26.7 (11.4–36.9)
Dmin (Gy)	20 (12–25)	20 (8–25)	20 (8–25)
Fractions	1 (1–5)	2 (1–5)	1.5 (1–5)
Collimator diameter (mm)	15 (4.5–25)	12.5 (7.5–30)	15 (4.5–30)

Median values are presented with ranges in parentheses

D_{max} maximal dose, D_{min} minimum marginal dose

Statistical analysis

The main endpoint of this study was to compare survival in the newly diagnosed and recurrent GBM patient groups (Kaplan–Meier test). The secondary endpoint was to analyze demographic, clinical, and radiosurgical treatment-related variables and identify those that may predict longer survival (Cox proportional hazards survival regression analysis). Two-sample *t* test was used to analyze the distributions between the two groups.

Results

The median survival from diagnosis for the patients treated with CyberKnife as an initial clinical therapy was 11.5 months (range, 2–33) compared to 21 months (range, 8–96) for the patients treated at the time of tumor recurrence/progression (Fig. 3). This difference was statistically significant (Kaplan–Meier analysis, $P=0.0004$). Only one patient (33 months survival) was alive in the newly diagnosed and two (19 and 28 months survival) in recurrent GBM patients at the time of the last follow-up. The median survival from the CyberKnife treatment was 9.5 months (range, 0.25–31 months) and 7 months (range, 1–34 months) for patients in the newly diagnosed and recurrent GBM groups (Kaplan–Meier analysis, $P=0.79$), respectively.

Cox proportional hazards survival regression analysis was performed to analyze potential prognostic factors that may have influenced this difference in length of survival. It demonstrated that none of the parameters such as the demographic factors, radiosurgical treatment parameters ($D_{\max}$, $D_{\min}$, number of fractions) or target volume, were predictive of longer survival.

The only other factor examined was the extent of surgical interventions, which had a significant effect on survival time ($P=0.008$), especially for patients who underwent biopsy vs. total tumor resection ($P=0.004$). Patients who underwent biopsy only had a median survival of 6 months (range, 5–20 months) compared to patients who had gross total resection with a median survival of 21 months (range, 8–96 months). There was no significant difference between the patients treated initially vs. at recurrence in the extensiveness of surgical interventions.

As mentioned above, RPA class was lower in the recurrent GBM group and although a strong tendency was observed for prediction ($P=0.07$), its effect on survival was not statistically significant. Likewise, EBRT doses were significantly different ($P=0.001$), with patients in the

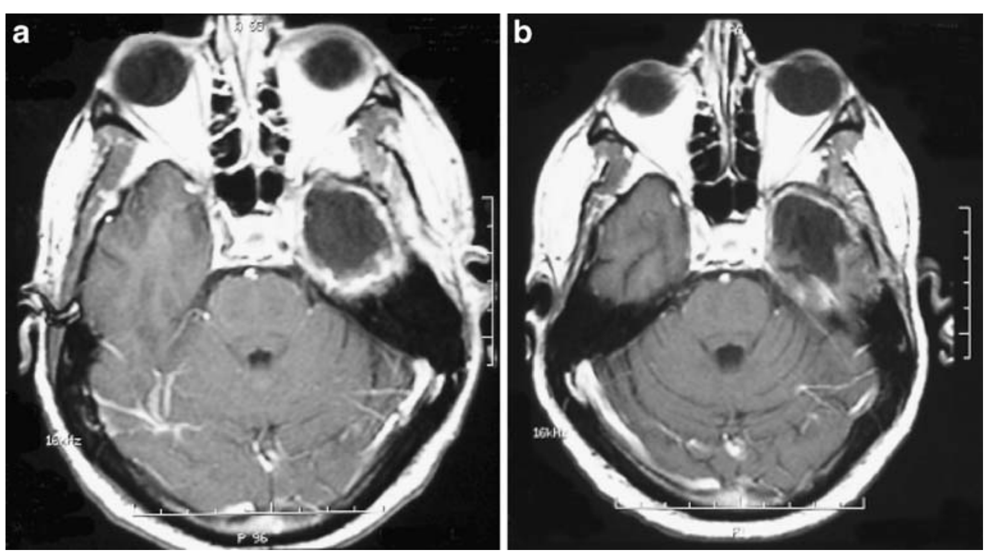

Fig. 2 **a** Pretreatment MRI with contrast. **b** Posttreatment MRI with contrast

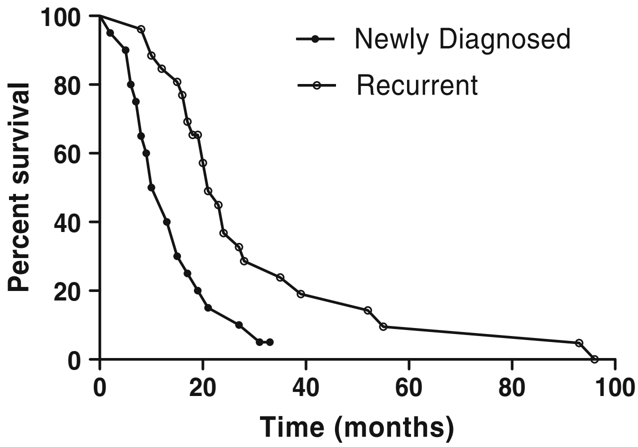

Fig. 3 The median survival from diagnosis for the patients treated with CyberKnife as an initial clinical therapy vs. for the patients treated at the time of tumor recurrence/progression

recurrent GBM group that were treated with higher radiation doses. However, this difference was not predictive of survival (P=0.2).

We also analyzed two groups of select patients who in our opinion benefited from stereotactic radiosurgery as primary or adjuvant treatment. There were five patients in the newly diagnosed GBM group who elected to not have EBRT and four out of them did not have chemotherapy either. Only one patient had total surgical resection, one biopsy was performed, and three patients had undergone subtotal resection. All these patients were treated with CyberKnife radiosurgery at 1 to 2 months from diagnosis. There were no statistically significant differences between this subgroup and the rest of the patients in the newly diagnosed GBM patient group, although they were slightly older (70.4 years; range, 58–81) and had lower average Karnofsky score (76, range 60–100), a higher RPA class (4.8, range 4–6), and larger tumors (9.2 cm^3; range 2.6–47.3 cm^3). This subgroup of five patients in the newly diagnosed GBM group had a median survival of 9 months (range, 2–33).

In addition, we analyzed another group of patients that survived 24 months or longer from the time of diagnosis. There were 14 patients in this group, five women and nine men. The average age was 58.9 years (range, 42–82 years). The median survival was 32 months (range, 24–96 months). There were no statistically significant differences in regards to age, RPA class, or radiosurgical treatment parameters between this subgroup and the rest of the patients, although it is worth noting that the median treatment volume was comparably smaller and measured at 3.5 cm^3 (range, 0.9–47.3 cm^3). When Cox proportional hazards survival regression analysis was performed to analyze factors that may have influenced this difference, the only factors were the extent of surgical interventions (P=0.02) and time to SRS treatment (P=0.0001). Twelve patients in this group had total gross resection and two patients had subtotal resection. The median time to CyberKnife treatment was 14 months (range, 1–89 months) for this subgroup of patients and 3 months (range, 1–16 months) for the remaining patients.

Discussion

The results of the present study may be most relevantly compared to the results of Gamma Knife studies, as the aim of both procedures is local tumor control achieved through noninvasive delivery of radiation. Gamma Knife stereotactic radiosurgery delivers conformal radiation to lesions using stereotactic head frames attached to the skull with screws, so it may not be considered an entirely noninvasive procedure.

In general, our results concur with the previously published Gamma Knife reports regarding the appropriate timing of SRS [13, 15, 33, 41]. It is not surprising that CyberKnife in addition to EBRT does not prolong survival of patients with newly diagnosed GBMs, because a highly malignant tumor theoretically should not require high doses achieved with SRS. We were not able to demonstrate any survival advantage for newly diagnosed GBM patients treated with CyberKnife, but considering the dismal success rate of the current multimodality treatment for GBM, CyberKnife radiosurgery as the primary and only treatment option for selected GBM patients deserves to be explored further. Although only five patients received radiosurgery as primary monotherapy, too few to make definite conclusions, it is noteworthy that their median survival time was comparable to that reported in the literature [36]. Survival times for patients who have undergone no treatment or only one conventional mode of treatment with any other treatment alone average at only 3 months [19, 27, 31, 34]. SRS can be offered as an option to patients who reject an extensive surgical procedure or who cannot tolerate radiation or decide against it. CyberKnife radiosurgery as a noninvasive and palliative option that does not require significant time commitment or cause many side effects may be the most suitable alternative in such cases. Therefore, CyberKnife treatment in place of conventional EBRT may provide comparable outcomes in significantly shorter treatment times, which is important in these terminally ill patients.

Future developments of SRS for glioma treatment should be focused on improving targeting and overcoming limitations of imaging techniques, which guide tumor targeting during treatment planning. Given that local recurrences of GBM occur even after aggressive multimodal treatment regimens, it is clear that infiltrative tumor cells are left untreated [3, 4, 15, 20, 22]. CT or MRI, often utilized in conjunction with one another, are the most common imaging techniques used for treatment planning. A significant limitation of both CT and MRI is that contrast enhancements are not necessarily indicative of tumor, as necrosis and edema are often indistinguishable from contrast enhancements due to the tumor per se. Thus, adding metabolic imaging alongside CT and MRI may help to distinguish tumor from necrosis or edema and more aptly guide treatment planning. Miwa et al. [26] investigated the extent of the overlap in tumor volumes in GBM patients using metabolic imaging (^{11}C-methyl methionine accumulation in positron emission tomography) and gadolinium enhanced T_1-weighted MRI. In a series of ten patients, the metabolic imaging tumor area was found to be larger than the MRI tumor area in all patients. In these patients, the MRI area encompassed only 58.6% of the metabolic area on average. Similarly, Chan et al. [5] recently performed a study that compared GBM tumor volumes delineated by proton magnetic resonance spectroscopy metabolic imaging studies and T_1-weighted MR imaging-derived radiosurgical target volumes for Gamma Knife SRS treatment of primary and recurrent GBM. The authors demonstrated that 12 of the 26 patients had less than a 50% overlap of tumor volume and treatment volume according to the two imaging methods. Patients whose imaging studies had more than 50% overlap were found to have a significantly longer median survival time (15.7 months) than those who lacked 50% overlap (10.4 months). Both of these studies suggest that metabolically active tumor cells consistently evade detection by conventional imaging strategies. Further, the fact that incorporation of metabolic imaging into Gamma Knife SRS treatment planning was found to be beneficial to patient survival may suggest that metabolic imaging studies could be useful for planning CyberKnife SRS as well.

Several clinical factors should be considered while evaluating reported survival times after SRS. In an effort to identify pretreatment prognostic variables that affect survival rates in GBM patients, Curran et al. [11] developed the RPA classification. The validity of RPA classification was confirmed by a later study [37], and survival times are often reported for patient groups in terms of these prognostic classes [18, 21, 23, 35]. When we stratified our patients according to RPA class, the difference between newly diagnosed and recurrent GBM patient groups was statistically significant. The relation between lower RPA class and longer survival times approaches significance. The extent of surgical intervention was also predictive of longer survival in our study, which had been previously demonstrated in GBM patients [9, 16]. It is unknown to what extent these factors have influenced the results of our study. As with any retrospective review, selection bias may also have played a role. Roberge and Souhami [33] have suggested that any apparent survival improvement in reported SRS phase I–II trials may be attributable to patient selection. However, even the best patient selection method that is based on clinical criteria only cannot entirely eliminate this problem. The invasive nature and extension of glioma cells through neural axes are predisposed by the underlying molecular genetics [32, 40]. The development of classifications based on the defined molecular profiles [29, 32] may better predict survival and thus contribute to an improved treatment decision-making process. Until new biologic strategies are in place to conquer this genetically coded information, efforts should be focused on rationally and individually designing treatment protocols customized to a patient's prognosis.

The fact that survival time was longer for the patients treated at the time of tumor recurrence was related to patient selection bias inadvertently associated with retrospective nature of the study. On the other hand, the subgroup of 14 patients were treated with SRS at the median time of 14 months and, in our opinion, benefited from all the aspects of this multimodal treatment. CyberKnife effectiveness as radiosurgical boost in select patients should be explored further in a prospective clinical study designed to control for multiple variables, based on the results of this retrospective study and considering that mainly two variables (the extent of surgical resection and timing of SRS) were predictive of longer survival time.

Conclusion

There is no apparent survival advantage in using CyberKnife in initial management of GBM patients. The present data suggest that it should be reserved for patients manifesting with local tumor recurrence/progression after conventional therapy.

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References

1. Adler JR Jr, Murphy MJ, Chang SD, Hancock SL (1999) Image-guided robotic radiosurgery. Neurosurgery 44:1299–1306 discussion 1306–1297
2. Ammirati M, Galicich JH, Arbit E, Liao Y (1987) Reoperation in the treatment of recurrent intracranial malignant gliomas. Neurosurgery 21:607–614
3. Burger PC, Heinz ER, Shibata T, Kleihues P (1988) Topographic anatomy and CT correlations in the untreated glioblastoma multiforme. J Neurosurg 68:698–704
4. Burger PC, Dubois PJ, Schold SC Jr, Smith KR Jr, Odom GL, Crafts DC, Giangaspero F (1983) Computerized tomographic and pathologic studies of the untreated, quiescent, and recurrent glioblastoma multiforme. J Neurosurg 58:159–169

5. Chan AA, Lau A, Pirzkall A, Chang SM, Verhey LJ, Larson D, McDermott MW, Dillon WP, Nelson SJ (2004) Proton magnetic resonance spectroscopy imaging in the evaluation of patients undergoing gamma knife surgery for grade IV glioma. J Neurosurg 101:467–475
6. Chang CN, Chen WC, Wei KC, Ng SH, Ho YS, Huang DY, Lee SP, Hong JH (2003) High-dose-rate stereotactic brachytherapy for patients with newly diagnosed glioblastoma multiformes. J Neurooncol 61:45–55
7. Chang SD, Adler JR (2001) Robotics and radiosurgery—the cyberknife. Stereotact Funct Neurosurg 76:204–208
8. Cho KH, Hall WA, Gerbi BJ, Higgins PD, McGuire WA, Clark HB (1999) Single dose versus fractionated stereotactic radiotherapy for recurrent high-grade gliomas. Int J Radiat Oncol Biol Phys 45:1133–1141
9. Ciric I, Vick NA, Mikhael MA, Cozzens J, Eller T, Walsh A (1990) Aggressive surgery for malignant supratentorial gliomas. Clin Neurosurg 36:375–383
10. Collins SP, Coppa ND, Zhang Y, Collins BT, McRae DA, Jean WC (2006) CyberKnife(R) radiosurgery in the treatment of complex skull base tumors: analysis of treatment planning parameters. Radiat Oncol 1:46
11. Curran WJ Jr, Scott CB, Horton J, Nelson JS, Weinstein AS, Fischbach AJ, Chang CH, Rotman M, Asbell SO, Krisch RE, Nelson DF (1993) Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. J Natl Cancer Inst 85:704–710
12. Deorah S, Lynch CF, Sibenaller ZA, Ryken TC (2006) Trends in brain cancer incidence and survival in the United States: surveillance, epidemiology, and end results program, 1973 to 2001. Neurosurg Focus 20:E1
13. Fiveash JB, Spencer SA (2003) Role of radiation therapy and radiosurgery in glioblastoma multiforme. Cancer J 9:222–229
14. Gannett D, Stea B, Lulu B, Adair T, Verdi C, Hamilton A (1995) Stereotactic radiosurgery as an adjunct to surgery and external beam radiotherapy in the treatment of patients with malignant gliomas. Int J Radiat Oncol Biol Phys 33:461–468
15. Halperin EC, Bentel G, Heinz ER, Burger PC (1989) Radiation therapy treatment planning in supratentorial glioblastoma multiforme: an analysis based on post mortem topographic anatomy with CT correlations. Int J Radiat Oncol Biol Phys 17:1347–1350
16. Hentschel SJ, Sawaya R (2003) Optimizing outcomes with maximal surgical resection of malignant gliomas. Cancer Control 10:109–114
17. Hochberg FH, Pruitt A (1980) Assumptions in the radiotherapy of glioblastoma. Neurology 30:907–911
18. Hsieh PC, Chandler JP, Bhangoo S, Panagiotopoulos K, Kalapurakal JA, Marymont MH, Cozzens JW, Levy RM, Salehi S (2005) Adjuvant gamma knife stereotactic radiosurgery at the time of tumor progression potentially improves survival for patients with glioblastoma multiforme. Neurosurgery 57:684–692 discussion 684–692
19. Hulshof MC, Koot RW, Schimmel EC, Dekker F, Bosch DA, Gonzalez Gonzalez D (2001) Prognostic factors in glioblastoma multiforme. 10 years experience of a single institution. Strahlenther Onkol 177:283–290
20. Kelly PJ, Daumas-Duport C, Scheithauer BW, Kall BA, Kispert DB (1987) Stereotactic histologic correlations of computed tomography- and magnetic resonance imaging-defined abnormalities in patients with glial neoplasms. Mayo Clin Proc 62:450–459
21. Kondziolka D, Flickinger JC, Bissonette DJ, Bozik M, Lunsford LD (1997) Survival benefit of stereotactic radiosurgery for patients with malignant glial neoplasms. Neurosurgery 41:776–783 discussion 783–775
22. Lunsford LD, Martinez AJ, Latchaw RE (1986) Magnetic resonance imaging does not define tumor boundaries. Acta Radiol Suppl 369:154–156
23. Mahajan A, McCutcheon IE, Suki D, Chang EL, Hassenbusch SJ, Weinberg JS, Shiu A, Maor MH, Woo SY (2005) Case-control study of stereotactic radiosurgery for recurrent glioblastoma multiforme. J Neurosurg 103:210–217
24. Masciopinto JE, Levin AB, Mehta MP, Rhode BS (1995) Stereotactic radiosurgery for glioblastoma: a final report of 31 patients. J Neurosurg 82:530–535
25. McDermott MW, Berger MS, Kunwar S, Parsa AT, Sneed PK, Larson DA (2004) Stereotactic radiosurgery and interstitial brachytherapy for glial neoplasms. J Neurooncol 69:83–100
26. Miwa K, Shinoda J, Yano H, Okumura A, Iwama T, Nakashima T, Sakai N (2004) Discrepancy between lesion distributions on methionine PET and MR images in patients with glioblastoma multiforme: insight from a PET and MR fusion image study. J Neurol Neurosurg Psychiatry 75:1457–1462
27. Nieder C, Grosu AL, Astner S, Molls M (2005) Treatment of unresectable glioblastoma multiforme. Anticancer Res 25:4605–4610
28. Nieder C, Andratschke N, Wiedenmann N, Busch R, Grosu AL, Molls M (2004) Radiotherapy for high-grade gliomas. Does altered fractionation improve the outcome? Strahlenther Onkol 180:401–407
29. Nutt CL, Mani DR, Betensky RA, Tamayo P, Cairncross JG, Ladd C, Pohl U, Hartmann C, McLaughlin ME, Batchelor TT, Black PM, von Deimling A, Pomeroy SL, Golub TR, Louis DN (2003) Gene expression-based classification of malignant gliomas correlates better with survival than histological classification. Cancer Res 63:1602–1607
30. Nwokedi EC, DiBiase SJ, Jabbour S, Herman J, Amin P, Chin LS (2002) Gamma knife stereotactic radiosurgery for patients with glioblastoma multiforme. Neurosurgery 50:41–46 discussion 46–47
31. Patwardhan RV, Shorter C, Willis BK, Reddy P, Smith D, Caldito GC, Nanda A (2004) Survival trends in elderly patients with glioblastoma multiforme: resective surgery, radiation, and chemotherapy. Surg Neurol 62:207–213 discussion 214–205
32. Rich JN, Hans C, Jones B, Iversen ES, McLendon RE, Rasheed BK, Dobra A, Dressman HK, Bigner DD, Nevins JR, West M (2005) Gene expression profiling and genetic markers in glioblastoma survival. Cancer Res 65:4051–4058
33. Roberge D, Souhami L (2003) Stereotactic radiosurgery in the management of intracranial gliomas. Technol Cancer Res Treat 2:117–125
34. Salcman M (1980) Survival in glioblastoma: historical perspective. Neurosurgery 7:435–439
35. Sarkaria JN, Mehta MP, Loeffler JS, Buatti JM, Chappell RJ, Levin AB, Alexander E III, Friedman WA, Kinsella TJ (1995) Radiosurgery in the initial management of malignant gliomas: survival comparison with the RTOG recursive partitioning analysis. Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 32:931–941
36. Sathornsumetee S, Rich JN (2006) New treatment strategies for malignant gliomas. Expert Rev Anticancer Ther 6:1087–1104
37. Scott CB, Scarantino C, Urtasun R, Movsas B, Jones CU, Simpson JR, Fischbach AJ, Curran WJ Jr (1998) Validation and predictive power of Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis classes for malignant glioma patients: a report using RTOG 90-06. Int J Radiat Oncol Biol Phys 40:51–55
38. Shrieve DC, Alexander E III, Black PM, Wen PY, Fine HA, Kooy HM, Loeffler JS (1999) Treatment of patients with primary glioblastoma multiforme with standard postoperative radiotherapy and radiosurgical boost: prognostic factors and long-term outcome. J Neurosurg 90:72–77
39. Silbergeld DL, Rostomily RC, Alvord EC Jr (1991) The cause of death in patients with glioblastoma is multifactorial: clinical

factors and autopsy findings in 117 cases of supratentorial glioblastoma in adults. J Neurooncol 10:179–185
40. Simon M, Ludwig M, Fimmers R, Mahlberg R, Muller-Erkwoh A, Koster G, Schramm J (2006) Variant of the CHEK2 gene as a prognostic marker in glioblastoma multiforme. Neurosurgery 59:1078–1085 discussion 1085
41. Souhami L, Seiferheld W, Brachman D, Podgorsak EB, Werner-Wasik M, Lustig R, Schultz CJ, Sause W, Okunieff P, Buckner J, Zamorano L, Mehta MP, Curran WJ Jr (2004) 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. Int J Radiat Oncol Biol Phys 60:853–860
42. Stieber VW, Bourland JD, Tome WA, Mehta MP (2003) Gentlemen (and ladies), choose your weapons: Gamma knife vs. linear accelerator radiosurgery. Technol Cancer Res Treat 2:79–86
43. Vordermark D, Kolbl O, Ruprecht K, Vince GH, Bratengeier K, Flentje M (2005) Hypofractionated stereotactic re-irradiation: treatment option in recurrent malignant glioma. BMC Cancer 5:55
44. Wallner KE, Galicich JH, Krol G, Arbit E, Malkin MG (1989) Patterns of failure following treatment for glioblastoma multiforme and anaplastic astrocytoma. Int J Radiat Oncol Biol Phys 16:1405–1409
45. Yu C, Jozsef G, Apuzzo ML, Petrovich Z (2003) Dosimetric comparison of CyberKnife with other radiosurgical modalities for an ellipsoidal target. Neurosurgery 53:1155–1162 discussion 1162–1153

Comments

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Villavicencio et al. report in detail a multicenter study of a small series of patients with the diagnosis of glioblastoma multiforme or its recurrence or progression after initial treatment and their survival rates after CyberKnife procedures. The conclusion that there is no apparent survival advantage in using CyberKnife in initial management of GBM patients is correctly drawn and important. There is also no disadvantage in using CyberKnife as a secondary option after this tumor recurs. However, the longer survival time for patients treated at the time of tumor recurrence (in a very small group) is certainly related to patient selection (as in almost all other recurrence studies), and therefore, further prospective studies should be done to compare CyberKnife and other modalities in recurrences to conclude possible advantages or disadvantages. This article demonstrated that radiation treatment avoids significant fixation methods compared to Gamma Knife. It is not significant for this study, but all presented tumors (by imaging) can be resected completely with adequate intraoperative imaging. Anyway, this paper is short, interesting, and noteworthy; therefore, the authors should be commended for their results and presentation.