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776 Survival Benefit of Stereotactic Radiosurgery for Patients with Malignant Glial Neoplasms Clinical Study

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ABSTRACT: **OBJECTIVE:** During an 8-year interval, we evaluated the survival benefit of stereotactic radiosurgery performed in 64 patients with glioblastomas multiforme (GBM) and 43 patients with anaplastic astrocytomas (AA).

METHODS: Adjuvant radiosurgery was performed either before disease progression or for recurrent tumor at the time of disease progression. Clinical and imaging follow-up data were obtained for all patients. The diagnosis of GBM was obtained by performing craniotomies in 41 patients and by performing stereotactic biopsies in 23. The diagnosis of AA was obtained by performing craniotomies in 19 patients (44%) and by performing biopsies in 24.

RESULTS: Of the entire series, the median survival time after initial diagnosis for patients with GBM was 26 months (standard deviation [SD], 19 mo; range, 5–79 mo) and the median survival time after radiosurgery was 16 months (SD, 16 mo; range, 1–74 mo). The 2-year survival rate was 51%. No survival benefit was identified for patients who underwent intravenously administered chemotherapy in addition to radiosurgery ($P = 0.97$). After undergoing radiosurgery, 12 patients (19%) underwent craniotomies and resections and 4 (6%) underwent subsequent radiosurgery for regional or remote recurrence. For 45 patients who underwent radiosurgery as part of the initial management plan, the median survival time after diagnosis was 20 months. Of the entire series, the median survival time after diagnosis for patients with anaplastic astrocytomas was 32 months (SD, 23 mo; range 5–96 mo) and the median survival time after radiosurgery was 21 months (SD, 18 mo; range 3–93 mo). The 2-year survival rate was 67%. Ten patients (23%) underwent subsequent craniotomies at a mean of 8 months after initial surgery, and two underwent subsequent radiosurgery. There was no acute neurological morbidity after radiosurgery. Histologically proven radiation necrosis occurred in one patient with GBM (1.6%) and two patients with AA (4.7%). For 21 patients for whom radiosurgery was part of the initial management plan, the median survival time after diagnosis was 56 months.

CONCLUSION: In comparison to historical controls, improved survival benefit after radiosurgery

was identified for patients with GBM and patients with AA. Although this survival benefit may be related to our selection of patients for radiosurgery based on their having smaller tumor volumes, no selection was made based on location. We observed that radiosurgery was safe and well tolerated. Its effectiveness as an adjuvant therapy deserves a properly stratified randomized trial.

KEY WORDS: Anaplastic astrocytoma; Glioblastoma multiforme; Malignant glioma; Radiation therapy; Radiosurgery

Malignant glial neoplasms of the brain are associated with poor outcomes. Multimodality management, including surgery, radiation therapy, boost irradiation techniques, and chemotherapy, seem to enhance survival and quality of life for appropriate patients^(10,21,27). Despite improvements in each of these treatments, most patients eventually die within 12 to 24 months as a result of disease progression. Factors that influence outcome include histological grade (glioblastomas multiforme [GBM] versus anaplastic astrocytomas [AA]), patient age, brain location, radiation dose, Karnofsky performance status, and surgical resectability^(6,33). In 1987, we initiated an evaluation of stereotactic radiosurgery as a less invasive method to boost the tumor radiation dose⁽⁹⁾. Initial criticisms of the use of radiosurgery for malignant gliomas included its focal radiation delivery⁽¹⁵⁾, and because it was performed in a single-session, the potential advantage of radiation delivery over multiple cell-cycle times (as achieved in brachytherapy) was not provided. However, the intense radiobiological effect of single-session radiation cell kill, regardless of mitotic phase, was our argument for the use of radiosurgery. Our hypothesis was that in comparison to historical controls, radiosurgery as an adjuvant technique would prove to be a safe and potentially effective adjuvant therapy for patients with GBM or AA.

PATIENTS AND METHODS

Gamma knife radiosurgery was performed in 64 patients with GBM and 43 patients with AA using the following entry criteria: mean contrast-enhanced tumor diameter <3.5 cm, age <75 years, Karnofsky performance score of ≥ 50 , any brain location, and proven histological diagnosis. This series comprised 6% of the total number of patients undergoing stereotactic radiosurgery at the University of Pittsburgh during our initial 8-year experience. Patients were informed that radiosurgery would be used to treat the contrast-enhanced portion of the tumor and not tumor infiltration beyond that border at the same dose. Early patients were informed of the use of radiosurgery for malignant brain tumors, such as brain metastases, reported from other centers. Informed consent was obtained from all patients.

GBM (n = 64)

For initial histological diagnosis, 41 patients underwent craniotomies and resections (64%) and 23 underwent stereotactic biopsies. The mean patient age

was 51 years (range, 3–72 yr), and the mean Karnofsky performance score was 90 (range, score of 50–100) at the time of radiosurgery. Forty-five patients (70%) were treated before disease progression (defined as within 8 mo of diagnosis). In this group, radiosurgery was part of an initial management strategy that included either postdiagnosis conventional fractionated radiation therapy plus radiosurgery or three cycles of continuous infusion of intravenously administered carmustine/cisplatin chemotherapy plus radiation therapy and radiosurgery (n = 47). In the latter case, radiosurgery was typically performed 5 to 8 months after diagnosis. The mean fractionated radiation therapy (tumor plus 3 cm) dose was 60 Gy. Nineteen patients with GBM (30%) were treated at the time of tumor progression (defined as tumor growth revealed by imaging ≥ 6 mo after completion of the prior treatment). For the entire group, the mean interval between diagnosis and radiosurgery was 10 months (range, 0–72 mo), which was 6.2 months for the group undergoing initial treatment and 18.9 months for the group experiencing recurrence.

The mean tumor volume (calculated using the dose-volume histogram) at radiosurgery was 6.5 ml (range, 0.88–31.2 ml). The 50% isodose line was used to cover the tumor margin in more than 90% of the patients (range, 40–90%). The mean dose delivered to the tumor margin was 15.5 Gy (range, 12–25 Gy), and the mean maximum dose was 30.5 Gy (range, 21.4–50 Gy). The tumors were located in hemispheric (lobar) locations in 58 patients (91%) and in deep (posterior fossa or diencephalon) locations in 6 patients.

AA (n = 43)

The mean patient age of this group was 45 years (range, 3–73 yr), and the mean Karnofsky performance score was 90 (range, score of 50–100). The histological diagnosis of AA was obtained by performing craniotomies and resections in 19 patients (44%) and by performing stereotactic biopsies in 24 patients (56%). Twenty patients (47%) underwent radiosurgery before disease progression (within 8 mo of diagnosis), and 23 patients were managed at the time of disease progression. Twenty-four patients (56%) underwent intravenously administered chemotherapy before undergoing fractionated radiation therapy. The tumors were located in lobar locations in 24 patients (56%) and in deep locations in 19 patients.

Stereotactic radiosurgery was performed at a mean of 3.9 months for the initial treatment group and 19.8 months for the disease progression group. The mean tumor volume at radiosurgery was 6 ml (range, 0.55–20.1 ml). The 50% isodose line was used to cover the enhancing tumor margin in more than 90% of the patients (range, 40–80% isodose). The mean dose delivered to the tumor margin was 15.2 Gy (range, 10–20 Gy); the mean maximum tumor dose was 30.4 Gy (range, 18.7–36 Gy).

Radiosurgical technique

All patients underwent stereotactic radiosurgery

while under local anesthesia, except children younger than 14 years who underwent radiosurgery while under general anesthesia. Between 1987 and 1991, patients underwent stereotactic computed tomography for tumor localization. Patients managed since 1991 underwent stereotactic magnetic resonance imaging for tumor definition. The edge of the contrast-enhanced portion of the mass was used to identify the tumor volume for radiosurgical targeting. For AA that did not exhibit contrast enhancement, we performed radiosurgery to the volume of long relaxation time signal change. The isodose configuration was made such that the selected treatment isodose enclosed the margin of contrast enhancement. Tumor cells beyond this rim of peripheral enhancement (within the low-density region observed on the computed tomographic scan or the high-signal region observed on the long relaxation time magnetic resonance image) were radiated at a dose below the peripheral selected isodose in the region of radiation falloff. Radiosurgery was performed collaboratively by a neurosurgeon, radiation oncologist, and medical physicist. The 201-source, cobalt-60 Leksell gamma knife was used for radiosurgery (Elekta Instruments, Atlanta, GA). All patients were discharged from the hospital within 24 hours of treatment and were given unchanged preoperative regimens of corticosteroid or anticonvulsant therapy. A single 40-mg intravenously administered dose of methylprednisolone was administered at the end of radiation. Initial imaging follow-up was performed 6 to 8 weeks after radiosurgery and then at 3- to 6-month intervals thereafter.

Statistical analysis

The product limit method of Kaplan and Meier was used to calculate actuarial rates of tumor control and freedom from cranial neuropathies⁽¹⁷⁾. Univariate comparisons of survival between patient groups were performed with the log rank test^(5,24). The Cox proportional hazards model⁽⁷⁾ was used for the stepwise multivariate analysis.

RESULTS

GBM

No patient was lost to follow-up. At the time of analysis, 34 patients had died and 30 were alive. Of the entire group, the median survival time after radiosurgery was 16 months (SD, 16.6 mo; range, 1–74 mo) (*Table 1*). The median survival time after initial diagnosis was 26 months (SD, 19 mo; range, 5–79 mo). When radiosurgery was performed at the time of tumor progression, the median survival time was 30 months after radiosurgery (SD, 13.3 mo; range, 2–74 mo). The 2-year survival rate from the time of diagnosis for the overall series was 51%. When radiosurgery was performed as part of the initial therapy in 45 patients, the median survival time after diagnosis was 20 months (SD, 2.6 mo; range, 5–76 mo). The 2-year survival rate for these patients was 41%. In this series, no survival benefit was identified for patients who had undergone intravenously administered chemotherapy in addition

to radiosurgery.

After radiosurgery, 48 patients (75%) required no additional surgical procedures. Twelve patients (19%) required delayed craniotomies and resections, and four patients (6%) underwent subsequent radiosurgery for either local progression or progression at a separate location. The mean time to craniotomy after radiosurgery was 5 months (subsequent radiosurgery, 7 mo). In 11 of 12 patients who underwent craniotomies after radiosurgery and radiation therapy, the histological findings included a mixture of viable tumor and necrosis with radiation effect. In one patient, only total necrosis without tumor was observed.

AA

No patient was lost to follow-up. Twenty-three patients were alive, and 20 had died. The median survival time after radiosurgery was 21 months (SD, 17.6 mo; range, 3–93 mo). The median survival time after tumor diagnosis was 32 months (SD, 22.7 mo; range, 5–96 mo). For the 23 patients who had undergone radiosurgery at the time of disease progression, the median survival time after radiosurgery was 31 months (SD, 11.8 mo; range, 3–47 mo). The 2-year survival rate after diagnosis was 67%. No survival difference was observed for patients who had undergone intravenously administered chemotherapy before radiosurgery. For the 21 patients who had undergone radiosurgery as part of the initial treatment program, the median survival time was 56 months after diagnosis (SD, 8.9 mo; range, 9–93 mo). The 2-year survival rate was 88%.

After radiosurgery, 31 patients (72%) required no additional surgical procedures. Ten patients (23%) underwent craniotomies and resections a mean of 8 months after radiosurgery. Pathological findings included a mixture of viable tumor and radiation changes in eight patients and total tumoral radiation necrosis in two. Two patients (5%) underwent subsequent radiosurgery for regional tumor progression.

Morbidity

No patient suffered acute neurological morbidity after radiosurgery, and no patient suffered seizures after treatment. All patients were maintained on stable doses of corticosteroid medication that were slowly tapered as tolerated. One patient (1.6%) with GBM developed delayed onset neurological symptoms specifically related to radiosurgery. This 35-year-old man with a left temporal glioblastoma developed increasing dysphasia and magnetic resonance evidence of an enlarging mass associated with regional edema. Image-guided resection of the mass confirmed the diagnosis of radiation necrosis.

Two patients with AA (4.7%) developed new neurological morbidity related to radiosurgery. One 14-year-old male patient with a biopsy-proven midbrain tumor developed a temporary Parinaud's syndrome; he made a full recovery after 1 year and had no imaging evidence of tumor at 93 months after radiosurgery. A second patient, a 26-year-old man

with a parietal tumor, developed new headaches and focal sensory seizures 7 months after radiosurgery. A magnetic resonance scan showed regional enhancement and high-signal change on long relaxation time images. A stereotactic resection was performed that disclosed a fibrous mass representative of radiation necrosis. The patient maintained a Karnofsky score of 100 and had no imaging evidence of tumor 48 months after radiosurgery.

Comparison with the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis

Table 2 lists the results of multivariate analysis of variables suspected of influencing survival of the combined series of 107 patients. Table 3 shows the survival data of the 65 patients in this series who underwent radiosurgery as part of their initial therapy; the patients are divided into RTOG recursive partitioning classes⁽⁸⁾. This technique is valuable for comparing series data using clinical and histological stratification parameters. Neither the RTOG class nor the extent of surgery (needle biopsy versus resection) proved to be significant predictors of survival. Age was the factor that was most predictive of survival time after diagnosis and after radiosurgery. Table 3 compares the median survival time and 2-year survival rates of 65 patients who underwent radiosurgery at presentation and 1578 patients who were treated without radiosurgery in three RTOG trials, stratified according to RTOG class. This suggests that patients in RTOG Classes III through V benefit from radiosurgery and that patients in Classes I and II (AA with age <50 yr and normal mental status or age 50 yr and symptoms for >3 mo) do not.

DISCUSSION

Radiobiology of radiosurgery for glial tumors

During radiosurgery, a focused amount of radiation is delivered to an intracranial target in a single treatment session. For benign tumors, optimal results are achieved when the targeted tumor volume matches precisely the radiosurgery volume. In the case of a malignant glial tumor, this can not be achieved. Although the contrast-enhanced tumor volume identified on images can be irradiated using a conformal margin isodose during radiosurgery, the malignant tumor cells beyond those identified by contrast enhancement remain "outside" the radiosurgery volume⁽¹⁸⁾. This makes radiosurgery of malignant gliomas different from radiosurgery of arteriovenous malformations and benign tumors or even, perhaps, radiosurgery of metastatic tumors with comparatively smaller zones of regional infiltration. This is not to say that these peripheral malignant cells receive no irradiation during radiosurgery but that they exist in the falloff of radiation outside the selected isodose. It is likely that the biological effect of radiosurgery at these lower isodoses is low. Nevertheless, the performance of a focused surgical procedure to the volume of contrast enhancement, whether through craniotomy and tumor resection, brachytherapy, or radiosurgery, can provide potential benefits to the patient by improving the likelihood of

local control^(11,14,16,34). Because treatment failure usually occurs locally⁽⁴⁾, a local boost treatment might be expected to provide some benefit. For this reason, several groups have initiated malignant glioma radiosurgery programs^(22,25,26). Barker et al.⁽³⁾ reported extensive experience, from 1988 to 1993, with the use of fractionated radiation therapy (60 Gy) for adjuvant management of GBM. The median survival time for the patients in that series was 11.2 months, with a 2-year survival rate of 16%⁽³⁾. This modern comprehensive series of results after radiation therapy alone for glioblastomas is valuable as an historical control to compare the potential benefits of boost radiosurgery.

The radiobiology of radiosurgery is different from that of brachytherapy. In radiosurgery, radiation is delivered in a single session, usually during 10 to 60 minutes, depending on dose and dose rate. The biological effect of radiation delivery in this single session is high, and the goal is arrest of cell-division capability, irrespective of an individual cell's mitotic phase during irradiation. In brachytherapy (interstitial irradiation), a focal radiation dose is delivered during 4 to 6 days, and an attempt is thus made to exploit susceptibility of cells within the cell cycle^(1,13,20,23). Some authors think that a single fraction tumor margin radiosurgery dose of 16 Gy has a biological effectiveness that is similar to a 40-Gy brachytherapy dose delivered during 5 days, although the two are not directly comparable. Shrieve et al.⁽³¹⁾ compared radiosurgery (n = 72) with brachytherapy (n = 32) in patients with glioblastomas. The mean tumor volume at radiosurgery was 10.1 cc, and the mean margin dose was 13 Gy. One-third of their patients had undergone prior chemotherapy. Subsequent surgery after radiosurgery was performed in 22% of the patients, compared to 44% of the patients who had undergone brachytherapy; this rate was similar to that in the present study. The histological findings in these patients showed tumor and necrosis. The median survival time after radiosurgery for patients with recurrent tumors was 10.2 months, and the 2-year survival rate was 19%.

There has been no laboratory comparison using in vivo tumor models. However, we compared the effects of 35-Gy radiosurgery on the rat C6 glioma and a 10-fraction, 85-Gy fractionated dose calculated to be of biological equivalence⁽¹⁹⁾. In this controlled study, animal survival and reduction in tumor size were identical. However, more pronounced histological effects were observed in the group that underwent radiosurgery when a high maximum dose was delivered. Cytotoxic effects indicated an early and more direct effect of radiation in this malignant tumor model. In contrast, indirect vascular obliterative effects have been observed in benign tumor radiosurgery models. Thus, in an experimental model, radiosurgery was observed to provide a positive clinical and histological benefit for a malignant glial tumor⁽¹⁹⁾. Radiosurgery is appropriate as part of a management plan for patients with GBM or AA.

Selection bias and radiosurgery

The evaluation of selection bias is necessary before understanding the results after radiosurgery or any therapeutic tool used in the management of patients with malignant gliomas. Selection bias was observed to be an important factor predicting outcomes for patients suitable for brachytherapy⁽¹²⁾. Because brachytherapy candidates had to have lobar tumors without involvement of midline structures, no ventricular disease, a tumor diameter smaller than a prescribed upper limit, and a higher Karnofsky score (factors predictive of better outcome), it is important to address those factors pertinent to radiosurgery. In the present study, patients undergoing radiosurgery had tumor diameters generally less than 3.5 cm in diameter (smaller than what we would consider acceptable for brachytherapy), had Karnofsky performance scores above 50, and had histological confirmation of tumor type. However, adverse brain location was not an exclusion factor. Thus, the present series included patients with such potentially adverse prognostic factors as deep location (brain stem, diencephalon) or subependymal tumor involvement. In this analysis, we did not determine that location was a significant variable that correlated with survival (*Table 2*).

We did determine that patients treated at the time of later disease progression survived longer, because these patients had already lived long enough to warrant further therapy. For the patients who underwent radiosurgery as part of the planned initial care, the median survival time was 20 months and the 2-year survival rate was 41%. Even within this initial treatment group, the selection of the timing of radiosurgery may have been important in the survival result. When we divided this GBM group in half and studied the survival data for patients who had undergone radiosurgery within 4 months of diagnosis (n = 12; median survival time, 16 mo) and compared the data to those of patients who had undergone radiosurgery between 4 and 8 months after diagnosis (n = 29; median survival time, 30 mo), a significant difference was observed ($P = 0.03$). No difference was identified for patients with AA.

Since 1990, radiosurgery at the University of Pittsburgh was used as part of a prospective management plan, including preirradiation continuous-infusion chemotherapy (carmustine/cisplatin), fractionated radiation therapy to 60 Gy, and radiosurgery when appropriate. Although we did not observe that the addition of chemotherapy provided a significant survival advantage according to multivariate testing, future studies performed with prospective control groups will be required to assess the actual effect of individual factors and selection bias.

Effect on survival

To date, there has not been a randomized trial to study the effects of radiosurgery, nor has there been even a large single-center review. Masciopinto et al.⁽²⁵⁾ reported 31 patients who underwent radiosurgery for GBM using a linear accelerator (median survival time, 9.5 mo). The mean tumor volume was 16.4 cc, which is significantly larger than the 6.5-ml mean

volume observed in the present study. All patients underwent radiation therapy to 50 to 66 Gy and then radiosurgery. Regional recurrence occurred in 65% of the patients at a mean of 7 months. They concluded from their data that radiosurgery provided no survival benefit compared to surgery plus fractionated radiation therapy and that, most likely, this lack of benefit was attributed to larger tumor volumes⁽²⁵⁾.

On the other hand, Sarkaria et al.⁽²⁸⁾ reported more encouraging results after surgery, fractionated radiation therapy, and radiosurgery in the initial management of 115 patients with either GBM or AA⁽²⁸⁾. The tumor margin dose varied between 10 and 20 Gy. The median survival time for patients with glioblastomas was 91 weeks, and the 2-year survival rate was 38% (41% in the present series). For patients with AA, the median survival time was not reached in this series and the 2-year survival rate was 72% (similar to the 67% rate in our study). Disease progression was observed in 59% of the patients, and subsequent surgery was performed in 29% (again, similar to our study). In these patients, viable tumor was identified in 25 patients and radiation necrosis in 8 (7%). Stea et al.⁽³²⁾ observed no difference in survival data between 33 patients who had undergone brachytherapy and 19 patients who had undergone radiosurgery⁽³²⁾. However, in this limited series, the toxicity of radiosurgery was less a result that may have been caused by a relatively low median radiosurgery dose of 10 Gy.

In our series, we observed a low rate of total tumoral radiation necrosis (1.6% for GBM and 4.7% for AA). Nineteen percent of patients with GBM and 23% of patients with AA underwent resection after radiosurgery because of an increase in tumor volume and regional mass effect. In the majority of these patients, a mixture of viable tumor and radiation effect was identified. It is difficult to know the significance of each histological finding on the clinical and imaging progression observed. We think that subsequent surgery rates in the 20% range after radiosurgery should be expected. However, the onset of brain edema and neurological deficits from progressive mass effect caused by pure radiation necrosis was uncommon.

Shaw et al.⁽³⁰⁾ reported a combined linear accelerator and gamma knife series in 102 patients with malignant tumors in which toxicity was addressed. A primary brain tumor was observed in 37% of the patients; 63% had metastases. Tumor growth after radiosurgery occurred within the target volume in 42% of the patients, within adjacent brain in 17%, at other sites in 24%, and systemically in 18% (from metastases). Interestingly, fewer than 10% of the patients who were not on steroids at the time of radiosurgery required steroid use thereafter. Survival was not addressed in this study, nor were the results distinguished between GBM and AA.

To study the results of subsequent surgery after linear accelerator radiosurgery, Schwartz et al.⁽²⁹⁾ reported a series of patients. For patients with glioblastomas, they observed a median survival time after diagnosis of 18 months and after radiosurgery of 11 months⁽²⁹⁾. For the group of patients who

underwent subsequent surgery after radiosurgery, the median survival time was increased to 24 months after diagnosis and 16 months after radiosurgery⁽²⁸⁾. Thirty-one percent of their patients required surgery after radiosurgery at a mean time of 5.5 months. Although this percentage of patients requiring subsequent surgery was slightly higher than in our series, we attribute this mainly to the treatment of larger tumors.

We observed that the RTOG recursive partitioning classification was not a significant independent predictor of survival time after diagnosis or after radiosurgery in this study. Young patients (<50 yr) with AA in this study did not seem to derive survival benefit when coded according to the RTOG classification. There are several possible explanations for this. First, the patient population in this study is much more selective than that in the RTOG study; all of the patients in this series had limited disease suitable for radiosurgery, and 38% were selected only after they developed new tumor progression. Second, it is possible that the patients with poor prognoses in the RTOG classes derive a proportionally greater benefit from radiosurgery than do the patients in the better RTOG classes. Another possible explanation is that the RTOG recursive partitioning classification system is inadequate. Age was examined as a continuous variable in our multivariate analysis and proved to be the dominant factor predictive of survival. A recursive partitioning classification system that separates patients into more than two age groups might be better able to predict prognosis because of the overwhelming prognostic importance of this factor. However, we think that the designation of patients with small volume tumors as eligible or ineligible for radiosurgery with current available data is premature. Without a randomized clinical trial, it is difficult to know to what extent improved outcomes were affected by patient selection.

Radiosurgery for tumor progression

When clinical and imaging evidence of tumor progression is documented, management options for many patients are limited. When a lobar tumor progresses, craniotomy and resection (debulking) are often possible. Further fractionated radiation therapy cannot be administered without high risk to the surrounding brain. The safety of radiosurgery has been documented for both primary and secondary malignant brain tumors⁽³⁰⁾. Chemotherapy can be used, depending on the patient's medical condition and hematological status. Carmustine is the single agent most active against malignant gliomas, but it often has been used as an adjuvant therapy as part of a patient's initial tumor management. Other conventional cytotoxic agents, such as procarbazine, cisplatin, and carboplatin, have activity against gliomas, but response rates for recurrent disease rarely exceed 30%.

When an infiltrative malignant neoplasm is progressing, is a focused therapy, such as radiosurgery, appropriate? Because most tumor growth is caused by local progression, we hypothesized that a specific radiosurgical boost could

provide a significant survival benefit for patients with malignant gliomas. When radiosurgery was used at the time of progression, we observed that patients with glioblastomas survived a median of 30 months. Patients with AA survived a median of 31 months. As a well-tolerated, low-morbidity procedure with a less than 24-hour hospital stay, we think that radiosurgery provided a high level of expected palliation with minimal detrimental effect on quality of life. Thus, for selected patients with progressive small-volume malignant glial tumors after prior therapy, radiosurgery potentially provides safe and effective palliation with enhanced local growth control.

McDermott et al.⁽²⁶⁾ from the University of California at San Francisco, reported on the use of radiosurgery for recurrent GBM (n = 34) and AA (n = 12). The median survival time for patients with glioblastomas was 40.6 weeks and for patients with AA was 61.6 weeks. In contrast, Ammirati et al.⁽²⁾ reported the benefits of subsequent surgery for malignant gliomas for 35 patients with GBM. For this group, they observed an additional median survival time of 29 weeks compared to 61 weeks for patients with AA (n = 20). The use of radiosurgery for progressive tumors cannot be compared with the prolongation of survival after surgery, because in routine practice, these patients would be different in their clinical presentation. Patients who come to resection would tend to have a larger mass lesion that would require debulking, whereas radiosurgery used at recurrence would be for smaller volume tumors in more stable patients or for unresectable tumors in deep brain locations.

At present, we think that boost stereotactic radiosurgery is a safe and potentially effective adjuvant treatment for patients with newly diagnosed or progressive malignant gliomas. Should radiosurgery be part of the standard management of patients with malignant glial tumors? Prior reports have provided data regarding the use of radiosurgery in selected patient groups. Together with this analysis, we think there is now impetus for a properly randomized prospective trial.

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COMMENTS

Kondziolka et al. provide another detailed review of their radiosurgery experience at the University of Pittsburgh, this time related to the effect of radiosurgery on survival for patients with glioblastomas multiforme (GBM) and anaplastic astrocytomas (AA). As the authors indicate, the timing of the administration of radiosurgery has a significant influence on outcome, presumably related to selection bias. For their patients with GBM who had undergone radiosurgery within 4 months of diagnosis, the median survival time was 16 months, compared to 30 months for those who had undergone treatment 4 to 8 months after diagnosis. The results for the earlier treated group are similar to those

reported by others.

On the other hand, keeping in mind that the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis of prognostic factors was derived from patients who may not have been candidates for radiosurgical treatment, comparisons by RTOG Grades I through VI of the Pittsburgh series with the historical control group suggest an added benefit from radiosurgery. It is of note that in the Pittsburgh series, although younger age, smaller tumor volume, and better Karnofsky performance score correlated with improved outcome as expected, pathological findings did not. In a multicenter study of selection factors influencing survival after radiosurgery for gliomas, Larson et al. ⁽¹⁾ observed that the pathological grade was one of the five most important factors.

Regarding AA, the results of radiosurgery (or of any treatment), can be compared with the results of the prospective randomized trial of procarbazine, lomustine, and vincristine versus carmustine that was reported by Levin et al. ⁽²⁾. In that study, the median survival time for patients was 157.1 weeks (36.2 mo) for the group receiving procarbazine, lomustine, and vincristine, which is similar to the median survival time (32 mo) reported in this article for the patients with AA.

Kondziolka et al. critically analyze the results of radiosurgery for a variety of neurosurgical conditions. As with brachytherapy, a definitive answer regarding the survival benefit of radiosurgery for malignant gliomas will come from prospective, randomized trials, such as the RTOG 9305 protocol. This article is further evidence that we have come very close to our limits with technological advancements in radiation therapy in the treatment of malignant gliomas and that other therapies will be required for significant improvements in survival.

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Kondziolka et al. provide a thoughtful analysis of their experience with gamma knife-based stereotactic radiosurgical treatment in 107 patients with malignant gliomas (64 of whom had GBM). Significant controversy exists regarding the use of a focal technique, such as radiosurgery, in the treatment of a diffuse, infiltrative disease, such as malignant glioma. This article contributes to the growing literature that helps to define the appropriate usefulness of radiosurgery to benefit selected patients with gliomas (tumor diameter, <3.5-cm; age, <75 yr; Karnofsky performance score, >50) and offer significant enhancement of quality survival time ^(1-3, 5,6,10). Age, tumor size at time of radiosurgery, and performance status have arisen as important variables in selecting patients so that they may gain significant benefit from radiosurgery ⁽⁶⁾.

In the current study, the median survival time after diagnosis for the entire group of patients with GBM was 26 months (range, 5–79 mo). For patients with GBM who were treated at the time of recurrence at least 6 months after the initial treatment (19 of 64 patients), the median survival time after radiosurgery was 30 months (range, 2–74 mo). The median survival time after diagnosis for those treated with radiosurgery (45 of 64 patients) as part of their initial management (similar to our "up front" protocol) was 20 months (range, 5–76 mo). This is double the median survival time for historical matched controls in our analysis ⁽⁵⁾. These survival data compare favorably with those from our institution for glioblastomas treated initially ⁽⁵⁾ and at recurrence ⁽¹⁰⁾ with linear accelerator stereotactic radiosurgery.

Twelve of 64 patients with GBM (19%) in this study required delayed craniotomies for resection (median time to craniotomy, 5 mo after stereotactic radiosurgery). This is a lower rate than we observed in our recent review (66 of 214 patients with GBM [30.8%] who were treated with radiosurgery and who required subsequent surgery). We observed that tumor volume greater than 10.7 cm³ (the median) was significantly correlated with increased risk of the need for subsequent surgery 1 to 2 years after radiosurgery ($P = 0.02$) ⁽⁹⁾. Analysis of the benefit of subsequent surgery is very complex, with significant selection bias. Patients who did not undergo subsequent surgery include those with good tumor control and neurological function, as well as those whose tumor recurrence was deemed inoperable. In general, we try to obtain good tumor control with radiosurgery; subsequent surgery with resection of necrotic tumor is performed mainly to decrease steroid requirements and enhance neurological function several months after radiosurgery. The increased edema in those patients is generally caused by toxicity of necrotic tumor (not radiation dose outside of the treatment volume) and resolves within weeks to months of resection ⁽⁹⁾.

Eleven of 12 patients requiring subsequent surgery had a mixture of necrosis and tumor; only 1 had pure necrosis. Half of our patients who underwent subsequent surgery had necrosis only within the treatment volume. The lower rate of necrosis in the

current study is surprising when considering the higher doses used by Kondziolka et al. compared to ours (15.2 Gy peripheral and 30.4 Gy central in this series versus 15 Gy peripheral and 18.8 Gy central in our series)⁽⁹⁾. However, we have actively used single photon emission computed tomography to aid in the selection of patients with low tumor activity for subsequent surgery, biasing our group toward having more patients with necrosis only.

We have observed thallium-201 C1 and technetium-99m hexametzime dual isotope single photon emission computed tomographic scans to be indispensable in evaluating patients after radiosurgery for malignant gliomas. We use this modality for management decisions, such as the exact location of tumor recurrence versus radiation change or necrosis, which is very difficult to determine based on computed tomographic and magnetic resonance scans^(4,7,8). Image fusion of single photon emission computed tomographic data into the computed tomographic or magnetic resonance three-dimensional reconstructions used for surgical planning and guidance has been of benefit in improving the safety and efficacy of resection.

Kondziolka et al. stated that there was no selection bias for location. Six of 64 GBM (10%) and 19 of 43 AA (44%) were in deep locations (diencephalon or posterior fossa). For example, in 10 thalamic GBM that we treated using radiosurgery, the median survival time was 20 months after radiosurgery (range, 3–47+ mo), indicating a significant role even in deep locations. Three of these patients underwent biopsies and then standard fractionated radiation and aggressive radiosurgical boost (12 Gy to the 80% isodose surface) and "planned" early subsequent surgery for more definitive resection several weeks later.

Radiosurgery for gliomas is often a complex endeavor, with appropriate use of aggressive surgery blended in with radiosurgery for the optimal management of these difficult cases. I agree with the authors that there is now enough data showing the effectiveness of radiosurgery to gain local tumor control in malignant gliomas, providing impetus for a properly randomized prospective trial.

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Kondziolka et al. evaluate the effects of stereotactic radiosurgical boost treatments on 107 patients with malignant astrocytomas. The median survival time for patients with GBM after radiosurgical boost was 16 months. The median survival time for patients with AA was 21 months. Survival correlated, as in most other reports, with younger age, smaller tumor volume, and higher Karnofsky score. The authors attempted to control for selection bias by using the RTOG recursive partitioning technique. This analysis showed

improved 2-year survival rates for the Class III, IV, and V patients only.

The authors present another thorough, scientific analysis of their radiosurgery experience. I have only one minor area of concern. The authors do not seem to directly address the issue of morbidity related to radiosurgical boost. In the abstract, they cite three patients with histologically proven radiation necrosis. Yet they report 12 patients with GBM who had "a mixture of viable tumor and necrosis" and 10 patients with AA who underwent subsequent surgery with no mention of pathological analysis. Most articles on brachytherapy and radiosurgery boost report subsequent surgery for any evidence of necrosis as a complication of therapy. Typically, 20 to 40% of patients are affected. It is extremely important that this high risk of morbidity from therapy be recognized.

We currently regard radiosurgical boost therapy for malignant gliomas to be an investigational modality of treatment with significant risks. As the authors indicate, selection bias can account for much of the benefit of any new therapy for gliomas. We agree with the authors' call for a properly randomized, prospective study.

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Plate 1 from *Essai d'Anatomie*. . . depicting subcutaneous craniocervical facial muscular groups.

*From, Jacques Gautier D'Agoty, *Essai d'Anatomie, en Tableaux Imprimés qui Représentent au Naturel Tous les Muscles. . . de la Tête. . . d'après les Parties Disséquées & Préparées par Monsieur Duverney*. Paris, 1745 (courtesy of Irwin J. Pincus, M.D., Beverly Hills, CA).*

Plate 1. *From, Jacques Gautier D'Agoty, *Essai d'Anatomie, en Tableaux Imprimés qui Représentent au Naturel Tous les Muscles...de la Tête...d'après les Parties Disséquées & Préparées par Monsieur Duverney*. Paris, 1745 (courtesy of Irwin J. Pincus, M.D., Beverly Hills, CA).*

Timing From	Histology	Median Survival	2-Year Survival (%)	3-Year Survival (%)
Diagnosis	GBM	26 mo	51	30
Radiosurgery	GBM	16 mo	38	21
Diagnosis	AA	32 mo	67	40
Radiosurgery	AA	21 mo	49	32

^a GBM, glioblastomas multiforme; AA, anaplastic astrocytomas.

Table 1. Survival after Radiosurgery for Malignant Glioma^a

Factor	Improved Postdiagnosis Survival (P Value)	Improved Postradiosurgery Survival (P Value)
Younger age ^b	0.0001	0.0008
AA versus GBM	0.03	0.19
Biopsy versus craniotomy	0.41	0.26
Smaller tumor volume ^b	0.17	0.02
Margin dose ≥ 16 Gy	0.64	0.50
Lobar location	0.95	0.98
Karnofsky score ≥ 70	0.004	0.001

^a AA, anaplastic astrocytomas; GBM, glioblastomas multiforme.
^b Continuous variable.

Table 2. Multivariate Analysis of Factors Related to Survival after Radiosurgery for Malignant Glioma^a

RTOG Grade ^b	Pittsburgh Radiosurgery			RTOG		
	Number	Median Survival (%)	2-Year Survival (%)	Number	Median Survival (%)	2-Year Survival (%)
I	13	37	67	139	59	76
II	2	5	50	34	37	68
III	13	39	73	175	18	35
IV	11	16	24	457	11	15
V	24	19	26	395	9	6
VI	2	7	0	263	5	4

^a RTOG, Radiation Therapy Oncology Group.
^b Grade I: anaplastic astrocytomas, normal mentation, and age <50 yr; Grade II: anaplastic astrocytomas, age >50 yr, Karnofsky performance scores of 70 through 100, and symptoms for >3 mo; Grade III: age <50 yr, anaplastic astrocytomas plus abnormal mentation, glioblastomas multiforme, and Karnofsky performance scores of ≥90; Grade IV: glioblastomas multiforme, age <50 yr, and Karnofsky performance scores of <90 or age >50 yr, Karnofsky performance scores of >70, and anaplastic astrocytomas for <3 mo or glioblastomas multiforme after resection; Grade V: age >50 yr, Karnofsky performance scores of ≥70, glioblastomas multiforme after resection, and radiotherapy of >54 Gy or Karnofsky scores of <70 with normal mentation; Grade VI: age >50 yr, Karnofsky scores of <70, and abnormal mentation or radiotherapy of <54 Gy after resection.

Table 3. Radiation Therapy Oncology Group Grades Compared with University of Pittsburgh Survival Rates in Patients with Malignant Gliomas^a