

Radiation necrosis following gamma knife surgery: a case-controlled comparison of treatment parameters and long-term clinical follow up

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Object. Radiation necrosis is the only significant complication of gamma knife surgery (GKS). The authors studied treatment plan parameters in patients who had radiation necrosis to determine if risk factors for necrosis could be identified.

Methods. Between September 1994 and December 1998, 286 patients were treated with GKS by the senior author. Of the 243 patients who were suitable for analysis, 17 developed radiation necrosis and were prospectively followed. Concurrently, 17 patients without necrosis were randomly selected as case controls on the basis of histological findings in their lesions. Integral dose–volume histograms (DVHs) were calculated and dose–volume treatment parameters were determined. A comparison was made with both the established Kjellberg and Flickinger isonecrosis risk lines. Clinical outcome was assessed according to time to resolution of symptoms and return to normal radiographic appearance.

Conclusions. Treatment plan variables associated with the risk of necrosis were increased tumor volume (TV) integral dose, increased TV, and increased 10-Gy volume. Other risk factors included repeated radiosurgery to the same lesion and glioma histological findings. The Kjellberg 1% risk line predicted a 5% risk of radiation necrosis and the Flickinger 3% risk line predicted a 3% risk. The median time to development of necrosis was 4 months, and symptomatic and radiographic recovery times were 7.5 and 10.5 months, respectively. The median survival time in patients with necrosis was 30 months. The authors recommend prospective TV determination and DVH calculation for all radiosurgical treatments and the avoidance of repeated radiosurgical treatments to the same lesion when possible.

KEY WORDS • radiosurgery • gamma knife • radiation necrosis • dose–volume histogram

STEREOTACTIC radiosurgery has been shown to be an effective, noninvasive treatment for a variety of intracranial conditions including benign and malignant tumors and AVMs. Stereotactic radiosurgery is most commonly delivered using a LINAC-based system or a gamma knife unit. Because open surgery is not required, the immediate complications occasionally seen with craniotomy, such as hemorrhage and infection, do not occur after radiosurgery. The primary risk associated with stereotactic radiosurgery is delayed radiation injury, which typically occurs 3 months or more after treatment and manifests itself as a necrotic lesion in the white matter.¹ Therefore, the goal of this modality is to deliver a high dose of radiation in a single fraction that is effective in treating the disease but does not result in radiation necrosis.

A number of risk factors have been identified for radiation injury after stereotactic radiosurgery. As expected, the

two most important factors are treatment volume and radiation dose. Kjellberg and Abe⁸ performed the pioneering studies and produced a plot of volume versus radiation dose that would predict a 1% chance of radiation necrosis. The Kjellberg and Abe original 1% isoeffect line has been reevaluated and is now thought to reflect more accurately a 3 to 8% risk of radiation necrosis.^{7,13} Using an integrated logistic formula, Flickinger and colleagues^{4,7} published a 3% isoeffect dose–volume curve that predicts brain necrosis. Both curves were constructed using little clinical data and require verification with actual patient outcomes. Nedzi, et al.,¹⁴ reported that complications associated with the use of a LINAC-based radiosurgery system for treatment of brain tumors were more common with higher doses, larger TVs, greater numbers of isocenters, and tumor dose inhomogeneity. Shaw, et al.,¹⁵ also showed that larger volumes, greater tumor dose inhomogeneity, and less conformal plans were associated with radiation injury.

The purpose of this study was to determine if the dose–volume relationships in GKS treatments were significantly different in patients who experienced radiation necrosis compared with patients without necrosis. We performed an integral DVH analysis in 17 patients identified as having radiation necrosis and compared them with 17 case-

Abbreviations used in this paper: AVM = arteriovenous malformation; DVH = dose–volume histogram; GKS = gamma knife surgery; LINAC = linear accelerator; MD/PD = maximum dose/peripheral dose; MR = magnetic resonance; PIV = prescription isodose volume; TV = tumor volume; TVID = TV integral dose; WBRT = whole-brain radiation therapy.

TABLE 1
Treatment plan characteristics in 34 patients who underwent GKS*

Parameter	Median Value (range)		p Value
	Tumors W/ Necrosis (17 patients)	Tumors W/O Necrosis (17 patients)	
WBRT (no. of patients)	11.0	12.0	NS
patient age (yrs)	52.0 (16–68)	41.0 (16–73)	NS
no. of isocenters	4.0 (1–9)	1.0 (1–7)	NS
margin dose (Gy)	20.0 (10–30)	18.0 (10–25)	NS
prescription isodose (%)	50.0 (40–75)	50.0 (45–80)	NS
PIV/TV	1.9 (1.3–4.9)	2.3 (1.4–4.0)	NS
TVID (mJ)	135.0 (18.5–1509)	40.6 (5.2–373.8)	0.02
TV (cm ³)	4.4 (0.36–28.8)	1.5 (0.16–17.6)	0.04
mean dose (Gy)	28.6 (18.2–53.3)	26.2 (13.3–45.3)	NS
10-Gy total volume (cm ³)	28.4 (3.4–83.2)	7.8 (1.3–42.7)	0.007
10-Gy normal brain volume (cm ³)	19.8 (2.6–61.9)	7.1 (1.1–25.1)	0.005

* NS = not significant.

matched controls. We then applied both Kjellberg and Abe's⁸ and Flickinger and colleagues^{7,13} models to our data. The clinical and radiographic outcomes after radiation necrosis were also studied.

Clinical Material and Methods

Patient Population

All patients treated with GKS by the senior author (L.S.C.) between September 1994 and December 1998 were prospectively followed and form the basis of this study. A total of 286 patients were treated, but 15 were lost to long-term follow up and were excluded from the analysis. All patients treated for trigeminal neuralgia were also excluded because the authors have not observed a case of radiation necrosis in this group. The remaining 243 patients were followed with regular evaluations and MR studies for at least 15 months or until they died. Seventeen patients developed radiation necrosis based on either of two criteria: pathological confirmation on MR imaging of radiation necrosis, or development of a necrotic lesion that resolved over time. Clinical and MR follow up was obtained every 2 or 3 months in patients with radiation necrosis until symptoms had resolved. To provide a comparison group, 17 patients with at least 15 months of follow up were selected to match the radiation necrosis group by the type of lesion treated.

An integral DVH was performed for each lesion treated in all 34 patients. The TVs were retrospectively drawn without knowledge of the treatment prescription plan. The following parameters were determined from the DVH: PIV; TV; PIV/TV ratio (a measure of dose plan conformity); TVID, mean tumor dose; 10-Gy total volume (the total brain and tumor volume receiving a dose of at least 10 Gy); and 10-Gy normal brain volume (perilesional brain receiving at least 10 Gy). Other data collected include the following: age; presence of diabetes; type of lesion; previous WBRT; number of isocenters; dose to the margin; and prescription isodose line. We did not assess tumor dose inhomogeneity because nearly all the patients were treated at the 50% isodose line and therefore had a MD/PD ratio

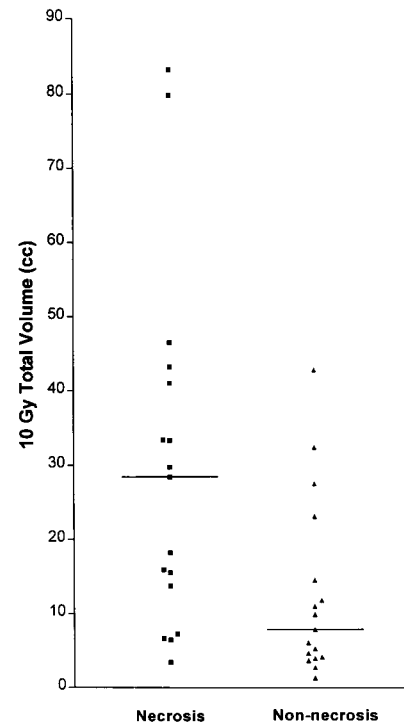


FIG. 1. Scatterplot of 10-Gy volumes, which were determined from treatment DVHs. The median value in each group is indicated by a horizontal line.

of two. For comparison with the Kjellberg and Flickinger isonecrosis risk lines, a theoretical diameter was calculated from the TV, assuming a spherical shape. Statistical analysis was performed using the Mann-Whitney U-test, and 2×2 contingency tables were analyzed using the Fisher exact test.

We obtained MR images in all 17 patients who developed radiation necrosis. The time to development of symptoms of radiation necrosis was recorded. Seven patients did not undergo surgical resection and were treated conservatively with corticosteroids. The time to resolution of clinical symptoms was recorded, as well as the time required for MR imaging to demonstrate resolution of radiation necrosis.

Results

Of a total of 243 patients constituting the population at risk, the disease distribution was as follows: 157 metastases, 36 gliomas, 40 benign tumors, and 10 AVMs. Of this at-risk group, 17 patients (7%) were known to have developed radiation necrosis; eight had brain metastases and three each had glioblastoma multiforme, astrocytoma, or meningioma. An additional 17 patients without necrosis who matched the radiation necrosis group for type of lesion were randomly selected.

Comparison of Treatment Plan Parameters

The treatment plan characteristics for the 34 patients studied are presented in Table 1. No significant differences between the two groups were found for the use of WBRT, age, number of isocenters, margin dose, treatment isodose, PIV/TV ratio, or mean dose. However, four vari-

TABLE 2

Comparison of treatment variables in two patients who served as their own internal controls

Case No.	Tumor Status	Margin Dose (Gy)	Isodose (%)	No. of Isocenters	PIV/TV	TVID (mJ)	TV (cm ³)	Mean Dose (Gy)	10-Gy Total Volume (cm ³)
1	necrotic	18	75	1	2.1	18.5	0.8	23.1	3.4
	nonnecrotic	18	50	1	2.6	4.9	0.2	22.3	0.7
2	necrotic	20	50	5	1.8	164.4	6.1	30.4	29.7
	nonnecrotic	22	90	1	4.9	10.6	0.5	23.6	7.2

ables were significantly different. Patients who developed necrosis had a higher total dose (135 mJ compared with 40.6 mJ) as measured by TVID. The TV was also significantly larger in patients with radiation necrosis (4.4 cm³ compared with 1.5 cm³). The most significant differences were seen in the two variables that were used to examine the volume enclosed by the 10-Gy dose. A scatterplot of the 10-Gy total volume shows that although the median values are significantly different (28.4 cm³ compared with 7.8 cm³), there still exists considerable overlap (Fig. 1). These results show that the dose–volume threshold for developing radiation necrosis may be quite low in some patients.

Illustrative Cases of Necrosis

The cases of two patients were instructive because they developed concurrent radiation necrosis in one area while a tumor in a different area of the brain was successfully treated (Table 2).

Case 1. This patient presented with metastatic non-small cell lung cancer and two lesions in the brain. At her 3-month follow-up visit, both lesions had responded, as seen on radiographic studies. Fourteen months after radiosurgery, she developed radiation necrosis in the right frontal lobe, for which the symptoms resolved with steroid treatment alone in 2 months; complete radiographically confirmed recovery took 8 months (Fig. 2). During the same period, the other lesion in the left frontal lobe remained quiescent. The margin dose to both lesions was identical (18 Gy) and both were treated with a single isocenter. The mean dose across the TV was nearly identical. The conformal nature of the two plans was similar, with the lesion that developed necrosis being slightly more conformal (PIV/TV, 2.13 compared with 2.61). The most significant differences on the side with radiation necrosis were as follows: increased total dose (TVID, 18.5 mJ compared with 4.9 mJ); larger TV (0.8 cm³ compared with 0.22 cm³); and larger 10-Gy total volume (3.4 cm³ compared with 0.74 cm³). The actual isodose curves and DVH calculated for this patient are shown in Fig. 3.

Case 2. This patient presented with metastatic ovarian carcinoma consisting of two lesions. The lesion that developed necrosis was treated twice (at a 1-year interval) and the patient developed symptoms 3 months after the second treatment. A comparison of the two lesions at the patient's initial treatment once again shows differences in treatment parameters. The margin dose was similar, but the tumor that developed necrosis was larger (6.1 cm³ compared with 0.45 cm³) and required more isocenters to treat (five compared with one). Conformity was again better for the necrotic lesion (PIV/TV, 1.79 compared with

4.89). The excessively high PIV/TV in this case is partly due to a volume averaging error that occurs in very small lesions. For the necrotic tumor, the TVID was higher (164.4 mJ compared with 10.6 mJ) and the 10-Gy volume was higher (29.7 cm³ compared with 7.2 cm³). Recovery from radiation necrosis took 16 months in this patient and was incomplete.

Among the 17 patients who developed necrosis, four (23.5%) underwent repeated treatments to the same region, whereas in none of the 17 case-controlled patients without necrosis were repeated treatments applied to the same area. In fact, in the entire group of 226 patients without necrosis, only one (0.4%) underwent a repeated treatment to the same tumor. A 2 × 2 contingency table made using the Fisher exact test shows that this difference is highly significant ($p < 0.0001$). Patients with gliomas were more likely to develop necrosis (six [17%] of 36) than patients with metastases or benign tumors (eight [5%] of 157 and three [7.5%] of 40, respectively). The difference was statistically significant according to the Fisher exact test ($p = 0.03$).

Comparison With Established Isoeffect Necrosis Risk Lines

We plotted our dose-volume data against Kjellberg and Abe's 1% and Flickinger and colleagues' 3% isoeffect necrosis risk lines to determine their predictive value (Fig. 4). The TV measured from the treatment plan MR image was converted into diameter by using the formula $(4/3)\pi(d/2)^3$. Assuming that the 17 patients without necrosis are representative of the entire 226 patients in this category, according to the Kjellberg line 16 of 17 are below the line, representing a total of 213 patients. In the necrosis group, 11 of 17 are below the line; therefore, 11 of 224 yields a 5% necrosis risk predicted by the Kjellberg 1% line. By the Flickinger model, three of 17 patients without necrosis are below the line, representing 186 patients. In the necrosis group, six of 17 are below the line; therefore, six of 192 yields a 3% risk predicted by the Flickinger 3% line.

Clinical Outcome After Radiation Necrosis

The median time from the last radiosurgery treatment to symptomatic radiation necrosis was 4 months (range 2–14 months). The median recovery time was 7.5 months based on symptoms (range 2–16 months) and 10.5 months based on imaging studies (range 6–16 months).

Discussion

Gamma knife surgery has been shown to be effective in controlling brain tumor growth as well as occluding

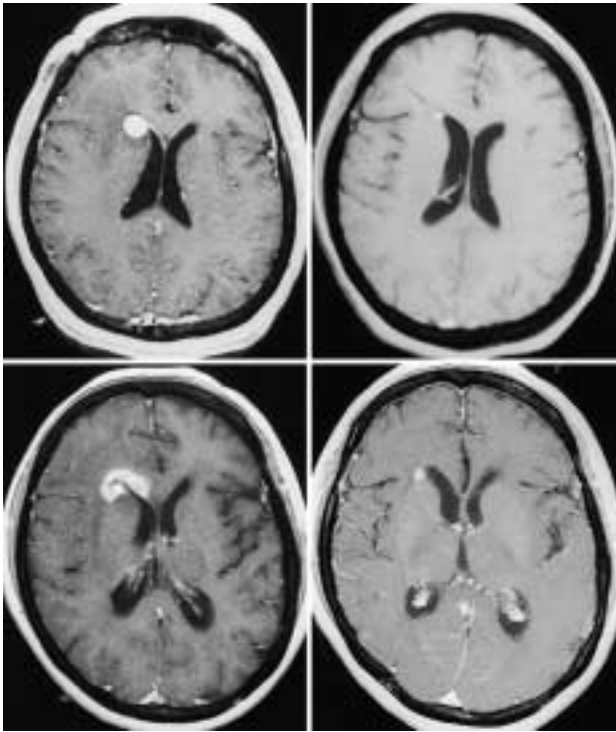


FIG. 2. Case 1. Axial MR images demonstrating the temporal course of radiation necrosis. *Upper Left:* Axial T₁-weighted MR image with contrast enhancement demonstrating a right frontal metastatic lesion before GKS. *Upper Right:* Three months later, the lesion has regressed, leaving a small residual area of enhancement. *Lower Left:* Fourteen months post-radiosurgery, radiation necrosis has developed in the region of the tumor. The dense residual tumor can be seen in the necrotic region and the overall lesion demonstrates minimal mass effect. *Lower Right:* Twenty-two months post-radiosurgery, the right frontal lesion has resolved, leaving residual enhancement and mild atrophy.

AVMs.⁹ This modality achieves this effect by delivering a high dose of radiation in a single fraction to a discrete volume. To understand the biological impact of a high single fraction of radiation, some relevant radiobiological principles must be understood. The relationship between cell death and radiation dose can be described by the following linear quadratic formula: $SF = \exp(-\alpha D - \beta D^2)$, where SF is the surviving fraction and the coefficient α relates the linear dose (D) and β relates the square of the dose.¹ Early-responding tissues such as cancer cells, bowel mucosa, and oropharyngeal epithelium have a high α/β ratio and are relatively insensitive to fraction size. Late-responding tissues such as benign tumors, normal brain, and spinal cord have a low α/β ratio and are more sensitive to fraction size. For this reason, conventional radiation treatments to the brain must be fractionated, because the brain's lack of tolerance dictates a small dose per fraction. The concept of the biologically effective dose is based on the α/β ratio and predicts that for a given single-fraction dose, the equivalent fractionated dose will be larger in late-responding tissues. A lower radiation dose in a benign brain tumor may have the same biological effect as a higher dose in a malignant one. These concepts should be taken into account when designing treatment plans and prescribing a radiation dose.¹⁰

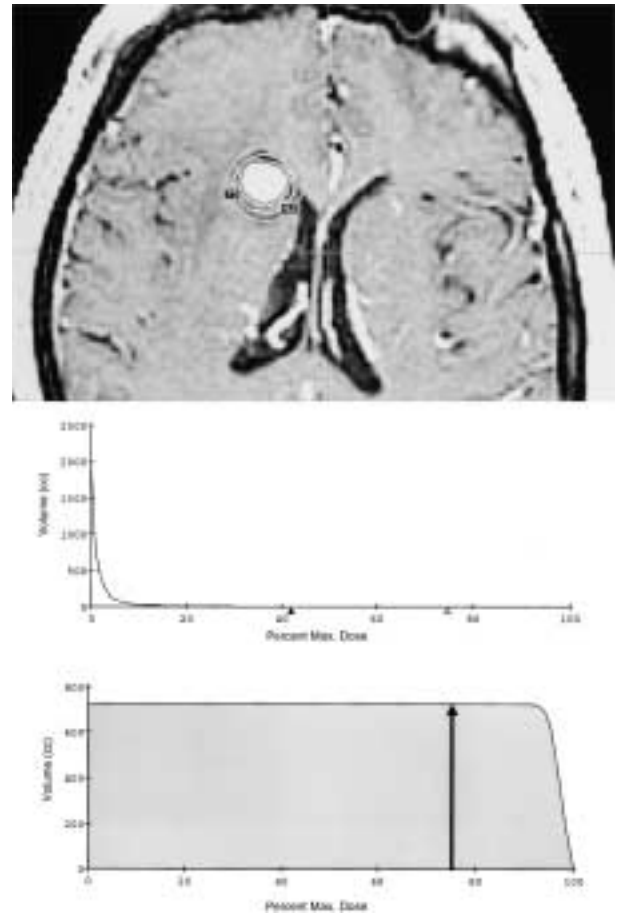


FIG. 3. Isodose curves and treatment parameters calculated from DVH. *Upper:* The T₁-weighted axial MR image from Fig. 2 upper left is shown with the isodose curves superimposed. The prescription isodose was the 75% line, and the 42% line corresponded to a dose of 10 Gy. *Center:* Graph showing the DVH calculated for the entire head volume. The PIV (1.7 cm³) is determined from the plot by finding the 75% mark (*open arrowhead*) and the corresponding TV. The 10-Gy volume corresponds to the 42% mark (*solid arrowhead*) and measures 3.4 cm³. *Lower:* Graph showing the DVH calculated for the TV. As evidenced from the graph, 100% of the TV (0.8 cm³) is treated at the 75% isodose line (*arrow*). The shaded volume under the curve represents the TVID.

Despite violating the rule regarding fractionation, radiosurgery succeeds in the brain because the dose is delivered to a small area and the highly conformal nature of the treatment minimizes the amount of normal brain exposed to radiation. Clearly, the risks associated with radiosurgery can be minimized if the dose is kept relatively low and the treatment volume is small.¹⁴ It is difficult to determine the parameter that most accurately describes this potential risk. Our results indicate that the margin and mean doses were not significant, but the TVID or total radiation dose was statistically significant. We believe that this variable actually reflects TV, because the mean dose was very similar between the two groups. In fact, the TV was significantly greater in the group with radiation necrosis. The two most significant parameters, however, were total volume enclosed by the 10-Gy treatment line and perilesional brain volume enclosed by the 10-Gy line.

Gamma knife radiation necrosis

We believe that the 10-Gy volume is the single variable that most accurately describes the risks associated with radiosurgery because it takes into account radiation dose, TV, and treatment plan conformity.

Voges, et al.,¹⁶ reported similar findings for prediction of radiation-induced imaging changes after LINAC-based radiosurgery in meningiomas, skull base tumors, and AVMs. They noted that 10-Gy volumes greater than 10 cm³ were associated with a greater risk of radiation changes. Our results show that four of 17 patients with necrosis had a 10-Gy volume less than 10 cm³, compared with 10 of 17 patients without necrosis. The scatterplot (Fig. 1) illustrates the difficulty in relying on a single variable to predict the risk of necrosis. Despite the highly statistically significant differences, some overlap exists between the two groups.

Surprisingly, the treatment plan conformity variable, PIV/TV, was not significantly different between the two groups. This is in contrast with reports in which it is suggested that more conformal GKS plans, as judged by the increased number of isocenters used, are associated with fewer complications.^{5,6} Further confusing the issue is the report by Nedzi, et al.,¹⁴ which shows that toxicity in a LINAC-based system is significantly associated with an increased number of isocenters. Clearly, using isocenter number as a proxy for plan conformity in a multivariate analysis is not ideal. Compared with GKS, the relative difficulty involved in using multiple isocenters in a LINAC-based system indicates that this variable may be more closely related to lesion size than plan conformity. Close inspection of our PIV/TV results reveals that larger tumors often had more conformal plans (PIV/TV < 2) because they required more isocenters to cover the lesion. Small lesions were frequently treated with a single isocenter and the corresponding PIV/TV ratio was often worse. Volume averaging errors due to small tumor size relative to pixel size also make the PIV/TV ratio less accurate for a very small lesion. The effect of conformity, therefore, appears to be overshadowed by the greater importance of treatment volume in determining risk. This is not to suggest that creating a conformal plan is not important. In fact, it becomes more important as the tumor gets larger because the 10-Gy volume increases substantially if too much perilesional brain is included in the treatment plan.

We could not assess the role of tumor dose inhomogeneity in radiation necrosis risk because most GKS treatments are prescribed to the 50% isodose line, resulting in an MD/PD ratio of two. It is difficult to determine the importance of MD/PD and PIV/TV as independent variables because altering either value also affects the treatment volume. Accordingly, we did not perform a multivariate analysis of the various dose-volume parameters because these variables are often closely interrelated and may render such an analysis useless.

A powerful predictor of radiation necrosis was a repeated radiosurgical treatment to the same tumor. Four (23.5%) of the 17 patients who developed radiation necrosis had undergone two or more radiosurgical treatments to the same tumor and only one (0.4%) of 226 patients without necrosis underwent a repeated treatment to the same tumor. Patients should be advised of the risk of repeated GKS to the same lesion and conventional surgery should be considered for accessible recurrent tumors. Interesting-

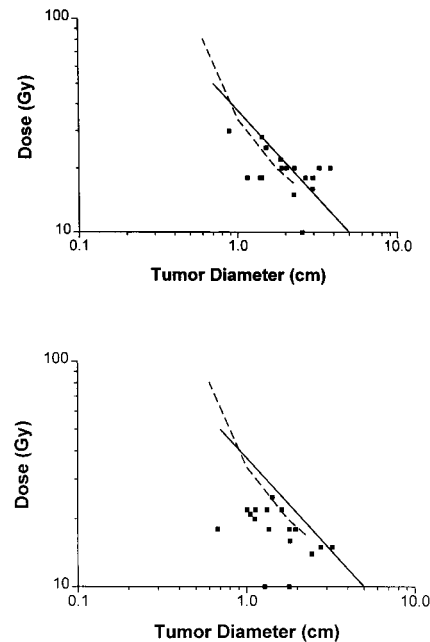


FIG. 4. Graphs comparing the Kjellberg 1% (solid line) and Flickinger 3% (dotted line) isonecrosis risk lines. Dose-diameter data in 34 patients studied using DVH were plotted against the aforementioned models. Upper: Data from 17 patients with necrosis. Lower: Data from 17 patients without necrosis. Our data confirm that the Kjellberg model predicts a 5% risk and the Flickinger a 3% risk. The squares represent the data points.

ly, previous WBRT did not predispose patients to radiation necrosis.

The lesion type was also a predisposing factor in radiation necrosis; gliomas were more likely to result in necrosis (17%) than brain metastases (5%) or benign tumors (7.5%). This confirms previous reports in which more radiosurgery complications are described in patients with glioma compared with those with metastases.^{2,12,15} As a rule, gliomas infiltrate into normal surrounding brain, thus guaranteeing that the radiosurgery target will include normal brain. Because normal brain is a late-responding tissue (low α/β ratio), the identical doses of radiosurgery are more injurious to brain cells than adjacent tumor cells, which are early responders (high α/β ratio).¹⁰ Brain metastases displace rather than infiltrate into the brain and involve less risk of significant irradiation of normal brain, provided that a small TV is treated with a conformal plan.

In two patients in our series an unusual situation occurred: one tumor responded completely to GKS, whereas another tumor site developed radiation necrosis. In both patients, the tumor in which radiation necrosis developed was the larger of the two, the one with a greater 10-Gy volume, and the one receiving a higher TVID. These results emphasize the nonstochastic nature of radiation necrosis. Specifically, a threshold for dose-volume exists for each patient that must be reached before necrosis will occur. Table 2 shows that the threshold may be quite different between patients. In the patient in Case 1, necrosis developed despite a TV of 0.8 cm³ and a 10-Gy volume of 3.4 cm³, both well below the median values for radiation necrosis. Because this patient did not have a predisposing medical condition like diabetes,³ other intrinsic fac-

tors may have sensitized her to the effects of radiation. The nonnecrotic lesion in the patient in Case 2 had a larger 10-Gy volume (7.2 cm³) than the lesion that developed necrosis in the first patient (3.4 cm³), thus indicating that the second patient had a higher threshold for developing radiation necrosis. Identifying the underlying genetic and molecular factors that predispose certain patients to radiation necrosis may provide new therapeutic targets against radiation injury.

There are few independent reports in which the clinical accuracy of Kjellberg and Abe's and Flickinger and colleagues' published isoeffect necrosis risk lines have been verified. Because both curves were constructed on theoretical bases, animal data, and some limited clinical information, neither curve was designed to predict radiation necrosis around cerebral lesions. Marks and Spencer¹³ reviewed the literature for radiation necrosis in AVMs and estimated that Kjellberg and Abe's 1% risk line actually represented a risk of between 3% and 8%. Ling, et al.,¹¹ conducted a similar review of the literature and estimated the true risk to be between 5% and 10.8%. Voges, et al.,¹⁶ applied their data on AVMs to the Kjellberg model and found the actual risk to range between 9.6% and 11.1%. The data in our series were heavily skewed toward intracranial tumors by the nature of the clinical practice. Our results confirm that the Kjellberg 1% risk line underestimates the potential risk of radiation necrosis but not to the extent noted in the AVM studies. We estimate a 5% risk of radiation necrosis when using their 1% line. The Flickinger integrated logistic model proved quite accurate when applied to our results and did predict a 3% risk of radiation necrosis as expected.

The latency period for the development of radiation necrosis and the time required for recovery that we report are comparable to those in previously published series.¹ Of the seven patients with radiation necrosis who did not undergo surgery for mass effect, six made a complete neurological and radiographically confirmed recovery; only one patient experienced some persistent deficits related to radiation necrosis. Corticosteroid medications were used in every case to help reduce symptoms related to cerebral edema. Considering that only three of 17 patients with radiation necrosis had a meningioma, the median survival was favorable (30 months). Four of eight patients with metastases are alive 8, 27, 30, and 60 months after GKS, and four of six patients with glioma are alive 18, 24, 27, and 65 months after GKS. Because the effects of radiation necrosis are usually reversible, the goal of tumor control should outweigh the desire to avoid this complication.

Physicians who use radiosurgery to treat intracranial lesions should understand the treatment plan parameters before delivering the radiation. This requires prospective TV determination and DVH calculation. The initial dose may be selected with the aid of either the Kjellberg or the Flickinger risk prediction model; however, many clinical situations dictate a more aggressive approach toward dosing. In these cases, we believe that the 10-Gy volume is the single parameter that most accurately describes the dose-volume relationship for a given treatment and may be used to assess the risk of radiation necrosis. A previous radiosurgical treatment to the same region substantially increases the risk, but previous WBRT does not. Patients with glioma are more likely to experience radiation injury

than those with metastases. On the positive side, patients may be reassured that their clinical outcome is unlikely to be adversely affected by the development of radiation necrosis.

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