Treatment of arteriovenous malformations with linear accelerator–based radiosurgery compared with Gamma Knife surgery

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Object. The authors sought to compare the outcomes of patients with arteriovenous malformations (AVMs) treated by Gamma Knife surgery (GKS) with those of patients treated by linear accelerator–based (LINAC) radiosurgery.

Methods. One hundred and eighty-seven patients with AVMs were treated at our institution between 1992 and 2003. Ninety-one patients were treated with GKS and 96 patients were treated with LINAC radiosurgery. Patient and treatment characteristics in the two groups included the following. In the LINAC group, the median age was 33 years (range 9–66 years); the median dose was 16 Gy (70% isodose line); the median treated AVM volume was 5.5 cm³; and 46% of patients in this group were treated after hemorrhage. In the GKS group, the median age was 38 years (range 6–63 years); the median dose was 20 Gy (50% isodose line); the median treated AVM volume was 4.3 cm³; and 44% of patients in this group were treated after hemorrhage. Obliteration of AVMs was determined by performing computed tomography (CT) angiography and/or magnetic resonance (MR) angiography and angiography. Patient follow-up evaluation included obtaining an MR angiogram/MR image or CT angiogram at 6 months, at 1 year, and then annually thereafter. Angiography was performed to confirm obliteration when MR angiography and/or CT angiography no longer revealed evidence of an AVM.

The 5-year estimated AVM obliteration rate was 66% in the entire patient group; the LINAC group was 60%; the GKS group was 72%; this difference was not statistically significant (p = 0.97). Twelve patients who underwent treatment with LINAC radiosurgery underwent retreatment with GKS and one was retreated with LINAC radiosurgery. The obliteration rate was 82%. Six patients treated with GKS were retreated with GKS, but the follow-up time is of short duration. Chronic toxicity occurred in 8% of both the GKS and the LINAC groups (p = 0.61). Posttreatment hemorrhage during the time of risk before AVM obliteration was 13% in the GKS group and 6.2% in the LINAC group (p = 0.05).

Conclusions. Treatment of patients with AVMs by using LINAC radiosurgery and GKS treatment produces high obliteration rates with acceptable long-term radiation toxicity in the patients treated.

KEY WORDS • arteriovenous malformation • Gamma Knife surgery • linear accelerator • radiosurgery

Stereotactic radiosurgery is a proven treatment option for AVMs.4,10,15,17 It is usually reserved for patients with AVMs that are located in deep-seated or eloquent areas of the brain or for patients deemed not to be surgical candidates.14 Stereotactic radiosurgery delivers high doses of ionizing radiation to the AVM target. Pretreatment neuroimaging often includes a combination of cerebral angiography, CT angiography, and MR angiography. Stereotactic radiosurgery provides the advantage of a high dose fall off outside the target volume, sparing normal brain tissues, as well as the ability to deliver dose distributions that are highly conformal and reproducible.18 Prior to undergoing imaging or SRS the patient is immobilized in a stereotactic headframe, which provides a high degree of positioning accuracy.

Stereotactic radiosurgery is performed using a high-energy LINAC, a Gamma Knife unit (Elekta Instruments AB, Stockholm, Sweden), and, less commonly, a charged-particle unit. Patient outcomes, levels of radiation toxicity, and rates of hemorrhage are well reported in the literature.2–5,8,10–13,15,16,19,21,23 A dose–response relationship exists between obliteration and toxicity.1,5,6,66
Larger AVMs are typically treated with a smaller dose to minimize toxicity to normal brain tissue, but also at the expense of decreasing the likelihood of obliterating the AVM.\(^4\) Linear accelerator–based radiosurgery has been performed more commonly, largely because LINACs are widely available and can be converted to deliver radiosurgical treatments. Gamma Knife units are less ubiquitous; however, they are becoming more commonly available in the US.\(^1\)\(^6\) Both modalities are successful in treating AVMs, although a direct comparison is difficult because of different patient characteristics and treatment techniques that often vary by treating institution.

In this report we summarize the results from a single institution in which we compare patients consecutively treated with LINAC SRS between 1992 and 2000 with patients consecutively treated with GKS between 2000 and 2003 in regards to obliteration rates, rates of hemorrhage, and radiation toxicity.

Clinical Material and Methods

One hundred ninety-nine patients with AVMs were treated at our institution between 1992 and 2003. Ninety-nine patients were treated with GKS and 100 patients were treated with LINAC SRS. Eight patients in the GKS group were lost to follow up and four patients in the LINAC group were lost to follow up, leaving 91 and 96 patients for evaluation, respectively. Between 1992 and April 2000, 96 patients were treated with LINAC SRS and available for review. In 2000, a Leskell Gamma Knife unit (model C; Elekta Instruments AB) was operational. Ninety-three patients with AVMs who had been treated with GKS were reviewed. In 2000, a Leskell Gamma Knife unit (model C; Elekta Instruments AB) was operational. Ninety-three patients with AVMs who had been treated with GKS were treated with LINAC SRS and available for review. In 2000, a Leskell Gamma Knife unit (model C; Elekta Instruments AB) was operational. Ninety-three patients with AVMs who had been treated with GKS were treated with LINAC SRS and available for review. In 2000, a Leskell Gamma Knife unit (model C; Elekta Instruments AB) was operational. Ninety-three patients with AVMs who had been treated with GKS were treated with LINAC SRS and available for review.

Patient characteristics (Table 1) and treatment characteristics (Table 2) of the two groups included the following. In the LINAC group, the median age of patients treated was 38 years (range 6–63 years); the median dose delivered was 20 Gy (50% isodose line); the median volume treated was 4.3 cm\(^3\); and 44% of patients were treated after hemorrhage. Actual AVM volumes were available for 55% of patients, in whom the median AVM volume was 3.8 cm\(^3\). Beginning in 2002 AVM volumes were routinely calculated, which allowed for the determination of a CoI (defined as total volume receiving the prescribed dose divided by total target volume receiving the prescribed dose). The median CoI was 1.1 in this group of patients, all of whom were treated with GKS. Thirteen patients had previously been treated with LINAC SRS, and four patients had been treated with GKS. The median follow-up time for patients treated with GKS was 32 months and it was 36 months for LINAC-treated patients.

Magnetic resonance imaging/MR angiography and/or CT angiography and angiography were performed to document AVM obliteration. The imaging protocol consisted of MR imaging/MR angiography or CT angiography at 6 months, 1 year after treatment, and then annually thereafter. Angiography was performed to confirm obliteration when MR imaging/MR angiography or CT angiography no longer demonstrated the AVM. The percentages of patients treated in the LINAC and GKS groups with more than 1-, 2-, 3-, and 4-year follow up were 94 compared with 88%, 77 compared with 81%, 55 compared with 50%, and 34 compared with 18%, respectively. The percentages of patients in the LINAC and GKS groups with AVMs treated in the cerebral hemisphere, basal ganglia, thalamus, midbrain, and brainstem were 81 compared with 92%, 4 compared with 4%, 9 compared with 3%, 4 compared with 0%, and 1 compared with 2%, respectively (Table 1). Pediatric patients, defined as those younger than 18 years at the time of treatment, accounted for 12.5% of the LINAC-treated patients and 9.5% of the GKS patients.

Statistical Analysis

The AVM obliteration rates were calculated using the Kaplan–Meier product limit method. The log-rank test (two-tailed) was used to evaluate statistically significant differences between the two groups. Univariate and multivariate analyses were performed using SPSS.

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**TABLE 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>LINAC</th>
<th>GKS</th>
<th>p Value</th>
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</thead>
<tbody>
<tr>
<td>median age in yrs (range)</td>
<td>33 (9–66)</td>
<td>38 (6–63)</td>
<td>0.07</td>
</tr>
<tr>
<td>male/female ratio</td>
<td>0.8:1</td>
<td>0.9:1</td>
<td>0.84</td>
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<td>prior bleed (%)</td>
<td>46</td>
<td>44</td>
<td>0.17</td>
</tr>
<tr>
<td>retreatment (%)</td>
<td>6.3</td>
<td>20</td>
<td>0.014</td>
</tr>
<tr>
<td>AVM site (%)</td>
<td>81</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>cerebrum</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>basal ganglia</td>
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<tr>
<td>thalamus</td>
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<td>3</td>
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<tr>
<td>midbrain</td>
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<td></td>
</tr>
<tr>
<td>brainstem</td>
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<td>2</td>
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</table>

**TABLE 2**

<table>
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<th>Variable</th>
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</tr>
</thead>
<tbody>
<tr>
<td>no. of isocenters</td>
<td>LINAC</td>
</tr>
<tr>
<td>median dose (Gy)</td>
<td>16 (13–29)</td>
</tr>
<tr>
<td>prescription isodose curve (%)</td>
<td>70 (50–95)</td>
</tr>
<tr>
<td>median treated vol (cm(^3))</td>
<td>5.5 (0.1–23.7)</td>
</tr>
</tbody>
</table>
Results

Obliteration Rates

Kaplan–Meier analysis of all (primary and retreatment) patients treated in both groups demonstrated 3- and 5-year obliteration rates of 21 and 72%, respectively, in the GKS group and 31 and 60% in the LINAC group; this result was not statistically significantly different \( p = 0.97 \); Fig. 1). When comparing patients in both treatment groups who had not been treated previously with SRS, the 5-year estimated obliteration rates were 71% in the GKS group and 61% in the LINAC group \( p = 0.67 \); Fig. 2). The 5-year estimated obliteration rates in those patients in both groups who had undergone prior SRS were 82% in the GKS group and 38% in the LINAC group \( p = 0.24 \); Fig. 3).

Interval to Obliteration

Fifty percent and 35% of the imaging-documented AVM obliterations occurred between 36 and 48 months in the GKS group and LINAC group, respectively. If the AVM had not been obliterated within 5 years, less than 5% in the GKS group and 12% in the LINAC group would ultimately become obliterated. The likelihood of obliteration was greater in the LINAC group; however, this result may be attributed to six patients in whom AVM obliteration was documented, but these patients had not undergone imaging at yearly intervals. Because most AVMs were obliterated between 36 and 48 months, a 48-month crude obliteration rate was calculated for both treatment groups. The crude rate was defined as the number of patients in whom AVM obliteration was demonstrated divided by the number of patients followed up for 48 months or longer or in whom AVM obliteration occurred before 48 months. The 48-month crude obliteration rate in the GKS group was 84 compared with 68% in the LINAC group.

Predictive Factors for AVM Obliteration

Age, sex, prescription dose, treatment status (initial compared with repeated treatment), and volume treated to prescription dose (proxy for AVM volume) were assessed by univariate analysis to determine if these factors were predictive of AVM obliteration (Table 3). Only dose and volume were significant in the LINAC group, whereas no statistical relationship was found in the GKS group. No factor was found to be predictive of response on multivariate analysis. If data in all patients were analyzed together, younger age and smaller volume treated to prescription isodose (proxy for AVM volume) were statistically significant as factors related to AVM obliteration on both univariate and multivariate analyses.
Dose Response for AVM Obliteration

Crude dose–response obliteration rates were calculated for all patients treated with either LINAC SRS or GKS. The crude dose was defined as the number of patients in whom neuroimaging demonstrated AVM obliteration divided by the number of patients followed up for 48 months or longer or in whom obliteration occurred before 48 months. For the entire cohort the crude rates of obliteration per dose were as follows: 13 Gy, 50%; 14 Gy, 0%; 16 Gy, 75%; 17 Gy, 71%; 18 Gy, 66%; 19 Gy, 100%; 20 Gy, 94%; and 22 Gy, 88% (Table 4).

Radiation Toxicity

Eight percent of patients in each group experienced chronic radiation toxicity (p = 0.61). Univariate analysis of factors related to chronic toxicity in the LINAC group was predictive only for patients who had undergone prior SRS. Multivariate analysis confirmed this finding in the LINAC group and was also predictive of toxicity in the GKS group (Table 5). The AVM treatment volume in those patients experiencing chronic toxicity differed in both treatment groups. In the GKS group, patients experiencing chronic toxicity had a median treatment volume of 8.7 compared with 4.1 cm$^3$ in those patients not experiencing chronic toxicity (p = 0.1). In the LINAC group, those patients experiencing chronic toxicity had a median treatment volume of 1.7 compared with 5.6 cm$^3$ in those not experiencing toxicity (p = 0.2). Whether the location of the AVM was related to toxicity was explored. In the GKS group, the location of the AVM was as follows: one in the thalamus, none in the midbrain, four in the basal ganglia, two in the brainstem, and 86 in the cerebral hemispheres. In the LINAC group, the distribution of treated AVMs was as follows: nine in the thalamus, four in the midbrain, four in the basal ganglia, one in the brainstem, and 78 in the cerebral hemispheres. In the GKS group there were eight patients who suffered from chronic toxicity: one of four patients with a basal ganglia AVM and seven of 86 patients with AVMs within the cerebral hemispheres. In the LINAC group there were seven patients who suffered from chronic toxicity: one of nine patients with AVMs in the thalamus, two of four patients with AVMs in the midbrain, one patient with an AVM in the brainstem, and three of 78 patients with AVMs in the cerebral hemispheres.

Posttreatment Hemorrhage

Posttreatment hemorrhage during the time of risk before AVM obliteration occurred in 12 patients (13%) in the LINAC group compared with six patients (6.2%) in the GKS group (p = 0.05). Six of 12 patients in the GKS group and two of six patients in the LINAC group had experienced hemorrhages before undergoing treatment. The median time to posttreatment hemorrhage was 9.5 months compared with 24.5 months in the GKS group and LINAC group, respectively. A total of five fatal hemorrhages occurred: three in the GKS group and two in the LINAC group. The median time to fatal hemorrhage after SRS was 10 months in the GKS group and 12.5 months in the LINAC group. The median treatment volume in patients who experience posttreatment hemorrhage in the GKS group was 3.7 compared with 4.5 cm$^3$ in those patients in whom no posttreatment hemorrhage occurred. In the LINAC group the median treatment volume in those patients experiencing a posttreatment hemorrhage was 10.7 compared with 5.4 cm$^3$ in those in whom no posttreatment hemorrhage occurred. The median dose delivered in patients experiencing a hemorrhage in the GKS group was 19 compared with 20 Gy in those patients who did not experience a hemorrhage. The median dose in the LINAC group was 15 Gy in those experiencing a hemorrhage compared with 16 Gy in those who did not.

Discussion

Stereotactic radiosurgery is a proven treatment option for patients who have surgically inaccessible AVMs.
The obliteration rates in the LINAC and GKS groups were not statistically different in our series. Both groups experienced the highest rates of obliteration between 3 and 4 years. Based on Kaplan–Meier estimates, both LINAC SRS and GKS offered excellent obliteration rates of 60% and 72% at 5 years, respectively.

There were two factors that were associated with an increased likelihood of AVM obliteration in the entire cohort of patients: young age and smaller treated volume. These findings are not dissimilar to those of other published series. A comparison of the treated volumes between the two groups revealed a median treatment volume of 5.5 cm$^3$ in the LINAC group compared with 4.3 cm$^3$ in the GKS group. The true AVM volume was not captured for the LINAC-treated patients due initially to the inability of the software to draw volumes, and in later years of the LINAC procedure it was because of physician practice. Fifty-five percent of patients treated with GKS had volumes drawn at the time of the procedure, and this practice became standard after 2001. As a surrogate for the actual volume, we have reported the treated volume, which is generally an overestimate of the true AVM volume, particularly for the LINAC group. This circumstance may explain the lack of correlation of volume with the rate of obliteration for the GKS group.

The toxicity of treatment was similar in both groups. In the LINAC group toxicity was reported in 8% of patients: four patients with radiation necrosis, two patients with motor dysfunction, and one patient with sensory dysfunction. Of the eight patients with reported toxicity, one patient had previously been treated with SRS. In the GKS group 8% of patients experienced toxicity: five patients with radiation necrosis and three patients with motor dysfunction. Of the seven patients who experienced chronic toxicity, four patients had been treated previously with SRS. We determined by multivariate analysis that the major predictor of chronic toxicity was prior SRS and that volume treated was not statistically significant, which is at variance with other reported series. The fact that dose and volume relationships were not predictive of toxicity may be attributed to the use of more tightly confined dosing based on previous studies. Although such a relationship has been reported in the literature, our doses prescribed to increasingly larger volumes are in accordance with other reports and below the expected threshold associated with toxicity.

The finding of similar toxicity rates in the two treatment groups may be related to several differences between the patient groups or treatment parameters. A major difference between the two groups was the median dose delivered. The median dose administered in the LINAC group was 16 compared with 20 Gy in the GKS group. This difference was largely due to different dose parameters in the LINAC group during the early years of our SRS program. As we gained more experience and additional studies were published, the median dose was increased. In addition, the use of the Gamma Knife model 4C with the automatic positioning system allowed for much better conformality compared with earlier models of the Gamma Knife and LINAC systems, which was also instrumental in maintaining similar toxicities despite increasing doses. Also during this time period, dose–volume relationships were being reported, and a greater understanding of the radiobiological effect of single-fraction therapy was being determined.

Another toxicity-related complication encountered was hemorrhage occurring after treatment with either LINAC SRS or GKS. A difference between the treatment groups was seen in the number of patients experiencing posttreatment hemorrhages in the period of risk after SRS. Thirteen percent of patients in the GKS group experienced bleeds compared with 6.2% of patients in the LINAC group. Two of the six LINAC-treated patients experienced hemorrhage after treatment, and six of 12 GKS patients experienced bleeds prior to SRS. Although there was a higher posttreatment hemorrhage rate in the GKS group, this rate was not associated with a higher rate of chronic toxicity. These findings are at variance with other reported lower hemorrhage rates, and we do not have a clear explanation for these observations. It is difficult to know whether the increased risk is related to previous bleeds or something inherent in the treatment itself. When comparing the treatment volumes in patients in whom hemorrhage occurred, the median volume was smaller in the GKS group compared with the LINAC group at 3.7 and 10.7 cm$^3$, respectively. The median dose in the GKS group was 19 Gy for those who experienced a hemorrhage and 20 Gy for those who did not experience a hemorrhage. In the LINAC group the median dose was 15 Gy for the patients who experienced a hemorrhage and 16 Gy for those who did not. We are unable to discern a dose or volume relationship in our data set that would be predictive for hemorrhage in the posttreatment period. There were no episodes of hemorrhage once obliteration of the AVM was documented.

Although the obliteration rates achieved with GKS are not statistically different from those achieved with LINAC SRS, there appears to be a trend in the curves favoring GKS. In addition, the higher degree of conformality that is achieved with GKS allows treatment of AVMs at higher doses without increasing the rate of radiation toxicity. In light of these factors, we treat all of our patients with AVM by performing GKS.

Conclusions

Gamma Knife surgery and LINAC SRS provided similar excellent obliteration rates of AVMs. Chronic toxicity rates were not significantly different between the two methods. The ease of treatment and the greater conformality achievable with GKS has made it our preferred modality for treating patients with AVMs.

References


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