ORIGINAL ARTICLE

Radiosurgical Retreatment for Brain Arteriovenous Malformation

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ABSTRACT: ***Objective:*** To analyze our experience with a second radiosurgical treatment for brain arteriovenous malformations (BAVMs) after an unsuccessful first radiosurgical treatment. ***Methods:*** Between 1993 and 2000, 242 patients were treated by the Toronto Sunnybrook Regional Cancer Center using a LINAC system. Fifteen of these patients required a second radiosurgical intervention due to the failure of the first procedure. Data was collected on baseline patient characteristics, BAVM features, radiosurgery treatment plan and outcomes. Brain arteriovenous malformation obliteration was determined by follow-up MRI and angiography and the obliteration prediction index (OPI) calculated according to a previously established formula. ***Results:*** The median interval between the first and second treatment was 46 months (range 39-109). The median follow-up after the second procedure was 39 months (range 26 to 72). The mean BAVM volume before the first treatment was 8.9cm^3 (range 0.3-21) and before the second treatment was 3.6cm^3 (range 0.2-11.6). The mean marginal dose during the first treatment was 18Gy (range 12-25) and during the second treatment was 16Gy (range 12-20). After the second treatment, nine patients had obliteration of their BAVM confirmed by angiography and one patient had obliteration confirmed by MRI, resulting in an obliteration rate of 66.6%, which is very comparable to that predicted by the OPI (65%). After the second treatment two patients had a radiation-induced complication (13.3%). ***Conclusion:*** Retreatment of BAVM using a second radiosurgery procedure is a safe and effective option that offers the same rate of success as the initial radiosurgery and an acceptable risk of radiation-induced complication.

RÉSUMÉ: Traitement radiochirurgical des malformations artério-veineuses du cerveau. ***Objectif:*** Analyser notre expérience de l'administration d'un second traitement radiochirurgical chez des patients atteints de malformations artérioveineuses cérébrales (MAVC) quand un premier traitement radiochirurgical a échoué. ***Méthodes:*** 242 patients ont été traités au Sunnybrook Regional Cancer Center de Toronto au moyen du système LINAC entre 1993 et 2000. On a dû avoir recours à une seconde intervention radiochirurgicale chez quinze de ces patients, vu l'échec de la première intervention. Nous avons recueilli les données initiales sur les caractéristiques des patients, les modalités du plan de traitement radiochirurgical et les résultats. L'oblitération des MAVC était évaluée par IRM et angiographie après le traitement et l'indice de prédiction d'oblitération (IPO) était calculé selon une formule pré-établie. ***Résultats:*** L'intervalle médian entre le premier et le second traitement était de 46 mois (écart de 39 à 109 mois). La durée médiane du suivi après la deuxième intervention était de 39 mois (écart de 26 à 72 mois). Le volume moyen de la MAVC avant le premier traitement était de 8,9 cm3 (écart de 0,3 à 21 cm3) et avant le second traitement de 3,6 cm3 (écart de 0,2 à 11, 6cm3). La dose marginale moyenne pendant le premier traitement était de 18 Gy (écart de 12 à 25 Gy) et de 16 Gy (écart de 12 à 20 Gy) pendant le second. Neuf patients avaient une oblitération de leur MAVC confirmée par angiographie après le second traitement et un patient avait une oblitération confirmée par IRM, soit un taux d'oblitération de 66,6%. Ce taux est comparable à celui prédit par l'IPO qui était de 65%. Après le second traitement, deux patients ont présenté une complication due à l'irradiation (13%). ***Conclusion:*** Le recours à un second traitement radiochirurgical dans les MAVC est une option sûre et efficace qui présente le même taux de succès que le traitement radiochirurgical initial ainsi qu'un risque acceptable de complications induites par l'irradiation.

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Brain arteriovenous malformation (BAVM) is an abnormal tangle of vessels that results in arteriovenous shunting of nonnutritive blood flow.[1] The detection rate for symptomatic BAVM is between 0.57-1.30/100,000 person-year and the prevalence, although unknown, is inferred to be lower than 10.3 per 100,000.[2] Once diagnosed, the main treatment objective is to obtain complete obliteration without creating a new neurological deficit. With advances in microsurgical, endovascular and radiosurgical treatments, this goal is more readily achieved.

It is now established that the best approach for BAVMs is to consider multimodality options comprising microsurgical resection, embolization and radiosurgery. These interventions are used either alone or in combination. The cure rate for patients receiving radiosurgery for BAVMs ranges from 53 to 86.6%.[3-12] The incidence of radiation-related complication ranges between

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2.4 and 9.4% using a Gamma-Knife or Linear accelerator system, with a period of 2 to 56 months for these complications to occur.[4,6,10,11,13,14] Fortunately, most of these complications are transient.

Patients treated with radiosurgery are often not good candidates for microsurgical or endovascular treatments. This factor prevents making a direct comparison between outcomes associated with radiosurgery and that of microsurgery or embolization for BAVMs. Furthermore, some patients who fail radiosurgical treatment remain poor candidates for microsurgical and embolization interventions. Although several studies have addressed the factors predictive of the complications and the success associated with radiosurgery in BAVMs,[4,5,14-27] few have focused on the outcome of the second radiosurgery. The objective of the present study is to analyze our own experience with radiosurgical retreatment for BAVMs using LINAC-based radiosurgery, and to provide a review of the literature on the retreatment results for BAVMs, highlighting the technical aspects and clinical results.

Material and Methods

The Toronto Radiosurgical Program

The LINAC radiosurgical program for BAVMs at the University of Toronto began in 1988, and between 1989 and 2000, 242 BAVMs were treated. The patients were initially reviewed by the Brain Vascular Malformation Study Group, a multidisciplinary team at the University of Toronto consisting of vascular neurosurgeons, endovascular radiologists and radiation oncologists. Those patients whose BAVMs were considered best treated by radiosurgery received treatment at the Toronto Sunnybrook Regional Cancer Center (TSRCC). At the TSRCC, radiosurgery is delivered using a 6-MV linear accelerator and the dynamic rotation technique described by Podgorsak et al.[28,29] Specific modifications have been made as described by O'Brien et al.[30] and Gillies et al.[31] These patients were followed with yearly Magnetic Resonance Imaging (MRI) and a Digital Subtraction Angiography (DSA) was performed at the three year follow-up. Patients with residual BAVM as shown on the DSA and/or MRI three years after the first radiosurgery treatment were again reviewed by the Toronto Brain Vascular Malformation Study group. Fifteen patients, representing approximately 20% of those with unobliterated AVMs, underwent a second radiosurgery between 1993 and 2000. All of these 15 patients had their first treatment at the University of Toronto except three: one who received Gamma-Knife radiosurgery, one LINAC radiosurgery and one Proton Beam radiosurgery. All patients had the second treatment at the TSRCC and were followed with MRI and DSA as described above.

The Procedure

At the TSRCC, the Dynamic Rotation LINAC based radiosurgery technique was used. During the procedure, an Olivier-Bertrand-Tipal stereotactic frame[32] (Tipal Instruments, Montreal, Canada) was applied to the patient's head under local anesthesia. Patients subsequently underwent an enhanced Computed Tomography (CT) scan of brain followed by stereotactic angiography. Images were transferred to radiosurgery software, which is a modification of the CMI software (Montreal Stereotactic Planning System, CMI Services, Montreal, Canada). Target definition, isocenters localization and dose planning were done by a neurosurgeon, radiation oncologist and physicist. Most patients were treated as outpatients, but some early patients were hospitalized over night. The above protocol was used for both the first and second treatment. In general, the same protocol of prescription was used for first and second treatments. Fifteen Gray (Gy) was given as a marginal dose at the 67% isodose contour in eloquent areas and 20 Gy at the 90% isodose in non-eloquent areas. In a very few large AVMs that could not be encompassed by a 3 cm collimator at the 67% isodose contour, the marginal dose was as low as 12 Gy.

Patient Outcome and Analysis

Complications were defined as either a direct consequence of BAVM hemorrhage or radiation induced injury. Any new or worse neurological symptom was considered secondary to radiation when not associated with hemorrhage. These complications were assessed by our team or, in the case of patients living outside of our city, by the neurologist/neurosurgeon involved in the treatment. Diagnosis of BAVM obliteration was made by total disappearance of the nidus, including any early filling veins on the angiography. The MRI diagnosis of BAVM obliteration was defined by the disappearance of any flow-voids in the area of the previously seen BAVM, in addition to the non-visualization of the nidus in the Magnetic Resonance Angiography (MRA). An attempt was made to ensure adequate follow-up and angiography based diagnosis of complete BAVM obliteration. The MRI based diagnosis of BAVM obliteration was used only in patients who refused follow-up angiography. The outcome and all the data pertinent to the treatment were collected in a spreadsheet (SPSS, version 9.0 for Windows) and reported as mean, median, maximum and minimum values, when indicated.

Results

Patient Population

The mean age of the 15 patients was 34 years (range 15-52 years) during the first treatment and 39 years (range 18-55 years) during the second treatment. The median interval between the first and the second treatment was 46 months (range 39-109 months). This group was composed of eight women (53.3%) and seven men (46.7%). The location of the BAVMs and Spetzler-Martin Grade at the time of the first and second treatments is shown in Table 1. The initial presentation was hemorrhage in nine patients (60%), seizures in four (26.7%) and headache in one case. In one patient, the BAVM was an incidental finding. Nine patients were intact before the first treatment. Among six patients with previous neurological signs, two had a motor deficit (13.3%), two had a memory deficit, one had a motor deficit and visual deficit (6.6%) and another one had a visual deficit.

Results after the First Procedure

During the first treatment the mean maximum diameter of the BAVM was 2.54 cm (range 0.7-4.1, median 2.73) and the mean volume was 8.9 cm^3 (range 0.3-21, median 8.30). The mean number of isocenters was 1 (range 1-3, median 1) and the median

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Table 1: BAVM location and Spetzler-Martin Grade before the first and second procedure

Location	*N*	*%*
Frontal	4	26.7
Parietal	2	13.3
Temporal	1	6.7
Occipital	1	6.7
Basal Ganglia	4	26.7
Corpus Callosum	3	20
Spetzler-Martin	*First Procedure*	*Second Procedure*
II	5(33.3%)	7(46.7%)
III	7(46.7%)	8(53.3%)
IV	3(20%)	-

reference isodose was 70% (range 50-100). The mean marginal dose was 18 Gy (range 12-25, median 15) and the mean maximum dose was 27 Gy (range 17-50, median 22).

In this group of 15 patients, two had previous open-surgery (13.3%) and six (40%) had previous embolization. Between the first and second radiosurgery, ten patients (66.7%) had a reduction in their volume (six patients less than 50% and four patients more than 50%). In the other five patients (33.3%) the residual BAVM was outside the first treatment plan. Between these five patients, two had a geographic missing: in fact, it was the portion outside of the first treatment that was not obliterated. In one patient, with an elongated AVM, it was recognized at the first procedure that part of the BAVM was outside of the marginal isodose and a staged treatment was planned. In the remaining two patients, the glue of the previous embolization obscured a small portion of the BAVM or a recanalization occurred. Summing up, all patients had an alteration in their BAVMs as a result of their first radiosurgery.

We divided the complications into permanent deficits (duration of symptoms more than six months) or transient deficits (less than six months). After the first radiosurgical procedure, only one patient (6.6%) had a permanent deficit. That patient had a posterior temporal BAVM measuring 3 cm in diameter that was initially treated with a LINAC system elsewhere (23 Gy marginal dose). She presented with quadrantanopia secondary to hemorrhage, which worsened to a homonymous hemianopia after the first radiosurgery, detected by formal visual field testing. This neurological deficit did not return to baseline after 109 months of follow-up before the second treatment. Two patients had bled between the first and second radiosurgery procedure, but both had complete recovery from these episodes.

Results after the Second Procedure

During the second treatment the mean maximum diameter of the BAVM was 1.68 cm (range 0.6-3.7, median 1.58) and the mean volume was 3.6 cm^3 (range 0.2-11.6, median 2.07). One isocenter was used in 14 cases and two isocenters in one case. The median reference isodose was 67% (range 60-100). The mean marginal dose at the second treatment was 16 Gy (range 12-20, median 15) and mean maximal dose was 21 Gy (range 17-22, median 22).

After the second treatment, nine patients had their BAVMs obliterated as confirmed by angiography (60%), two patients had bled after the second treatment and therefore had surgical resection of the BAVM before reaching the three year follow-up point (13.3%), three patients had residual BAVMs after three years (20%) and finally, one patient had the nidus obliterated as confirmed by MRI (6.6%). With MRI and angiography results taken together, the obliteration rate for our group of patients is 66.6%. Using the Obliteration Prediction Index (OPI – marginal dose (Gy) / lesion diameter (cm), developed by Schwartz et al.[33] the expected percentage of obliteration would be 65% (Figure).

After the second radiosurgery two patients had radiation-induced complications that were considered permanent deficits (13.3%). One had a memory deficit as the initial presentation that became worse following the second radiosurgery. This was formally assessed when the patient complained of memory loss that was affecting his daily activities. This patient had a corpus callosum BAVM and part of the fornix was included in the 67% marginal isodose in the second treatment. He was treated with a marginal dose of 25Gy in the first treatment and 15Gy in the second treatment. The second patient developed a new motor deficit that improved partially; this patient had a basal ganglia BAVM close to the internal capsule with a maximum diameter of 3.5cm during the first treatment and 2.7cm during the second treatment. She was treated by proton beam with a marginal dose of 16Gy in the first treatment and 15Gy by LINAC system in the second treatment. We have considered both complications as permanent (13.3%). Three patients bled within the first three

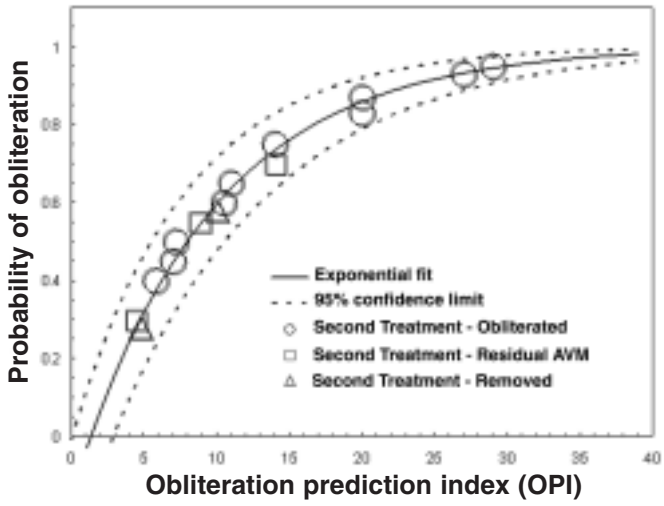

Figure: *The Obliteration Prediction Index (OPI) curve (33) and the OPI (marginal dose in Gy / BAVM maximum diameter in cm) for each patient during the second treatment.*

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years following the second radiosurgery, which is approximately a 6.8% annual risk (44.1 patients/year). However, two of these patients bled prior to the second radiosurgical procedure, suggesting that these BAVMs may have had a higher propensity to bleeding.

The mean follow-up after the second procedure was 43.8 months (range 26 to 72, median 39). The total follow-up since the first treatment was 96 months (range 76-156, median 93). There were no deaths during the follow-up.

Discussion

Although the radiosurgical retreatment of BAVMs has been performed for close to three decades,[34] the first report addressing specifically the outcomes in this group of patients was published in 1998,[35] followed by four other series after 2000.[6,36-38] The results of these studies, as well as the present study, are summarized in Table 2. This Table provides details about the number of cases, radiosurgery modality used, time interval between treatments, doses delivered, BAVM volume, in addition to the outcome and complication rates. The crude rates of obliteration and radiation induced complication (number of events divided by total number of patients in each series) are also tabulated. This calculation was done to allow weighting according to the size of each series.

We used the same protocol for the second radiosurgery as described previously for the first radiosurgery treatment of BAVMs.[8] In the present series, the median marginal dose in the second treatment was the same as the first treatment. A similar process has been described by other groups. Foote et al[37] described that the dose selection for retreatment was based primarily on target volume and location, regardless of prior treatment. Schlienger et al[38] have used the same standard protocol, based on dose-volume histograms, prescribing a peripheral dose of 20-25 Gy. Pollock et al.[6] have based the dose on the BAVM volume (4 cm^3, 20 Gy; 4–14 cm^3, 18 Gy; and >14 cm^3, 16 Gy), with the mean marginal dose being 18 Gy in both first and second treatment in their series. Maesawa et al[36] have also selected the dose based primarily on volume using integrated logistic formula guidelines. Karlsson et al[35] describe only the lowest dose given to retreated cases, which on average was 20 Gy. We chose to continue with the same protocol that we had used for the first treatments, as agreed upon by previously reported studies reviewed above, where they used their same protocols for first and second treatments.

In our series, after the second treatment, 60% of BAVMs selected to repeat radiosurgery showed angiography confirmed obliteration. This is comparable with the first treatment, where our angiographically confirmed obliteration rate was 60%.[8] It is of note that the OPI[33] was able to predict the rate of obliteration in our retreated patients. We found 66.6% of obliteration (considering DSA/MRI) to 65% of predicted obliteration. Although there was a decrease in the AVM volumes between the first and the second procedure, this fact was not enough to increase the obliteration rate, as predicted by the OPI.

If we apply the OPI using the median of the marginal dose and the median of the BAVM diameter (25 Gy and 3 cm, respectively, OPI=8.3) described by Schlienger et al[38] for their series, we would predict an obliteration rate of 58%. Indeed, they report an obliteration rate of 59%. This confirms that the OPI is able to predict the obliteration rate following the first radiosurgery using the LINAC system or Gamma-Knife as described before,[33] but it can also predict the chance of obliteration for the second radiosurgical treatment, describing the same biological effect of radiation after the second treatment. Unfortunately, in the other retreatment series, the BAVM diameter is not mentioned, therefore the OPI cannot be tested.

In our series, we found a 13.3% complication rate following the second radiosurgery. This may be inaccurate as our series is small, but it is essentially the same complication rate as for the larger population of treated patients from which this small group is drawn. The larger group of 244 patients had radiation-induced complications in 16.9%; transient in 9.6% and permanent in 7.4%[34] Karlsson et al[35] in their series at the Karolinska GK Centre had 12.5% complication rate after retreatment. Using the risk formula described by them before,[24,39] they concluded that a reasonably accurate risk estimation can be obtained by adding the risks from the previous treatment to the calculated risk for the present treatment (cumulative risk). On the other hand, Foote et al[37] report a 3.8% rate of complication in 52 patients treated, concluding that the overall complication rate after retreatment is not significantly different from overall complication rate for primary BAVM radiosurgery. The same authors argue that the prescription doses used at the Karolinska GK Center was higher than their doses and that many of the patients included in the Karolinska study were treated in the 1970s and early 1980s, prior to the application of advanced computer technology.

Maesawa et al[36] suggested that adverse radiation effects may be somewhat higher after a second radiosurgery treatment than cases not previously subjected to radiation. Schlienger et al[38] found that moderate parenchymal changes were more frequent after the second radiosurgical procedure than after the first procedure (88% vs. 57%). However, the frequency of necrosis-like changes was not significantly different between the first and second procedure. Compilation rates based on the six reported studies reviewed in this paper, including our own, estimates an 8 to 10% of complication rate (Table 2), which is an acceptable figure considering that the complication rate associated with other modalities of treatment for these BAVMs is higher.

Although the 2-4% annual risk of hemorrhage has been used to determine the likelihood of hemorrhage-free survival,[40,41] these calculations assume population homogeneity and uniform risk over time.[42] People who have bled are thought to carry a higher annual risk, with rates as high as 17.8% in the first year and 11.3% in subsequent years being reported.[43] Various factors such as sex, age, angioarchitectural findings, BAVM size and location have also been considered to define the annual risk of bleeding. The risk of bleeding during the latency period after the first radiosurgical treatment prior to obliteration ranges from 2.7 to 11.6%.[44-49] In this present series we found a 6.8% annual risk of bleeding within the first three years after the second radiosurgery. In our series, two of the three patients who bled within the first three years following the second radiosurgery had a history of prior bleeds. This may represent a selected group with a higher risk of hemorrhage. However, the patient numbers are too small to make definitive conclusions. There is insufficient evidence that a second radiosurgery changes the risk of BAVM hemorrhage during the latency period.

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Table 2: Previous series of second radiosurgical treatment for BAVM and present study

Author	Year	System	Number of Patients	Interval Between Treatments (months)	BAVM Volume (Second Treatment)	Marginal Dose	Percentage of Obliteration	Radiation Induced Complication	Death Radiat.-Related
Karlsson et al[35]	1998	GK	112	47 (13-196)	Mean $3.2cm^3$	Mean 20 Gy	64.3% (65/101)	12.5% (14/112)	0
Maesawa et al[36]	2000	GK	41	39.5 (30-56)	Median $1.9cm^3$	Median 17 Gy	71% (29/41)	4.8% (2/41)	0
Foote et al[37]	2003	LINAC	52	41 (36-70)	Mean $4.7cm^3$	Median 15 Gy	59% (24/41)	3.8% (2/52)	0
Schlienger et al[38]	2003	LINAC	32	52 (12-126)	Median $4.2cm^3$	Median 25 Gy	59% (19/32)	9% (3/32)	0
Pollock et al[6]	2003	GK	26	43 (-)	Median $4.3cm^3$	Median 16 Gy	86% (18/21)	12.5% (3/24)	0
Present study	2004	LINAC	15	46 (39-109)	Median $2.07cm^3$	Median 15 Gy	66.6% (10/15)	13.3% (2/15)	0
Average	**-**	**-**	**278**	**44.9**	**$3.44cm^3$**	**18.5 Gy**	**65.8%**	**9.4%**	**0**

The results found in our series are encouraging; especially because after the first unsuccessful treatment all cases were re-discussed in a multidisciplinary group and the final opinion was that the endovascular treatment or microsurgery carried a worse estimated morbidity risk for this group of patients. Considering that the radiation-related mortality of radiosurgery is zero in all series so far, and that the risk of morbidity is about 10% for retreatment, including eloquent or deep brain areas, we believe that this treatment should be considered for all patients. However, in patients where the reduction in size of BAVMs following the first radiosurgery treatment is sufficient to decrease the risk of microsurgery or allow a curative endovascular procedure, these treatments should be recommended as they offer the prospect of obliteration without a latency period. Even though BAVM microsurgery is always a challenging procedure, in our experience, BAVMs treated previously with radiosurgery have had a better plane of dissection and less bleeding, possibly due to endothelial proliferation, as well as partial or complete thrombosis of some vessels. The same finding has been described by other authors.[50] We consider the average of results shown in Table 2 as a good parameter to compare with other treatments during the decision-making process when the first radiosurgery has failed, as well as reasonable general figures that can be used for discussion with patients and their family.

A second radiosurgery treatment using a LINAC-based system for BAVM has the same rate of success with an acceptable risk of radiation-induced complications as the first radiosurgery treatment. Therefore, in patients where the first radiosurgery treatment has failed, a second radiosurgical treatment should be considered. We have found that the Obliteration Prediction Index (OPI), originally described for first treatments, applies to predict the results of the second treatments.

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