Radiosurgery for Arteriovenous Malformations: the University of Toronto Experience

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ABSTRACT: ***Background:*** From July 1989 to February 1996, 130 patients underwent sterotactic radiosurgery. We report the results of the first 50 patients eligible for a minimum of three years of follow-up. ***Methods:*** Twenty women and 30 men, (mean age: 37.5 years) were treated by dynamic rotation on a 6 MV linear accelerator. Prior treatment was embolization in seventeen, surgery in three and embolization and surgery in six. All had DSA and enhanced CT scanning, while some had MRI. Forty-seven treatments used a single isodose. Restricting eloquent normal tissue to 15 Gy, margin doses (at 50 - 90% isodose) were 12 Gy (one patient); 15 Gy (sixteen patients); 20 Gy (31 patients); 25 Gy (two patients). Maximum diameters were: < 1.5 cm (12 patients); < 2.0 cm (nine patients); < 2.5 cm (twelve patients); < 3.0 cm (thirteen patients; 3.0 cm (four patients). ***Results:*** Forty-five patients were evaluable at three years, with thirty-nine having angiography. Twenty-five had angiographically confirmed obliterations; two had parenchymal AVMs obliterated but with residual dural components; four had MRI evidence of obliteration (refused angiography). One patient acutely had a seizure; one patient (with hemorrhages, resection, and embolizations preceding two applications of radiosurgery, separated by 3.5 years) had worsening of memory. ***Conclusions:*** Our uncorrected (five patients unevaluable at three years) and corrected angiographically confirmed obliteration rates are 54% and 60% respectively. Our follow-up (98% accounting of cohort; 78% angiographic rate) and explicit derivation of denominators help delineate the efficacy of radiosurgery at these doses.

RÉSUMÉ: La radiochirurgie dans le traitement des malformations artério-veineuses: l'expérience de l'Université de Toronto. ***Introduction:*** De juillet 1989 à février 1996, 130 patients ont subi une radiochirurgie stéréotaxique. Nous rapportons les résultats des premiers 50 patients chez qui nous avons effectué un suivi minimum de trois ans. ***Méthodes:*** Vingt femmes et 30 hommes, (âge moyen: 37.5 ans) ont été traités par rotation dynamique sur un accélérateur linéaire de 6 MV. Une embolisation avait été effectuée antérieurement chez dix-huit, une chirurgie chez trois et une embolisation ainsi qu'une chirurgie chez six. Tous avaient eu une DSA et un CT scan avec rehaussement, alors que quelques uns avaient eu une RMN. Une isodose unique a été utilisée pour quarante-sept traitements. En limitant la dose au tissu normal à 15 Gy, les doses aux limites de la lésion (à 50 - 90% de l'isodose) étaient de 12 Gy (un patient); 15 Gy (16 patients); 20 Gy (31 patients); 25 Gy (2 patients). Les diamètes maximums étaient < 1.5 cm (12 patients); < 2.0 cm (8 patients); < 2.5 cm (13 patients); < 3.0 cm (13 patients); 3.0 cm (4 patients). ***Résultats:*** Quarante-cinq patients ont été évalués après 3 ans de suivi, dont 39 ont eu une angiographie. Vingt-cinq avaient une oblitération confirmée par l'angiographie; 2 avaient une MAV parenchymateuse oblitérée mais avec une composante durale résiduelle; 4 avaient des signes d'oblitération à la RMN (refus de l'angiographie). Un patient a fait une crise convulsive en phase aiguë; un patient, qui a présenté des hémorragies et a subi une résection et embolisations avant de subir deux radiochirurgies espacées de 3.5 ans, a présenté une détérioration de la mémoire. ***Conclusions:*** Nos taux non corrigés et corrigés d'oblitération confirmée par angiographie (5 patients non évaluables après 3 ans de suivi) sont de 54% et 60% respectivement. Notre suivi (98% de la cohorte; taux d'angiographie 78%) et notre dérivation explicite de dénominateurs aident à définir l'efficacité de la radiochirurgie à ces doses.

Can. J. Neurol. Sci. 1997; 24: 99-105

Arteriovenous malformations (AVMs) of the brain, regardless of how they present, are thought to confer a 4% annual risk of intracerebral or subarachnoid hemorrhage and an annual mortality rate as high as 1 per cent.[1] Since AVMs are often discovered in young people, the cumulative lifelong morbidity and mortality are considerable. Excision or obliteration have been shown to eliminate the risk of hemorrhage. The effect on epileptic seizures, headache and other symptoms is less clear.

In 1928, Cushing reported using several radiation treatments for an intracranial AVM and found it to have undergone almost complete intravascular thrombosis during the subsequent craniotomy to excise it.[2] Animal studies have been used to investigate the mechanism of radiation-induced obliteration of AVMs.[3] Doses of 30 Gy are associated with short latency focal tissue necrosis. Lower doses result in the proliferation of vascular endothelial cells, leading to thickening and ultimate thrombosis of pathological vessels after a longer latency period. Findings of thickened hyalinized vessel walls with luminal thrombosis have been consistently reported both in post-mortem histopathologic studies of AVMs treated with radiotherapy and in specimens from patients whose radiated AVMs were excised.[4]

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RECEIVED JULY 11, 1996. ACCEPTED IN FINAL FORM SEPTEMBER 26, 1996.

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There are several reported series of patients treated with fractionated external beam radiotherapy, generally at doses of 40 to 50 Gy. Patient numbers were small and treatment protocols were not systematic, making the results difficult to interpret.[5] Since the advent of radiation devices capable of very accurate localization and steep decline of off-target radiation, approximately 4,000 people with cerebral AVMs have been treated, mostly with a single fraction.[6] The procedure does not require a general anesthetic and bears a low morbidity and mortality. The major disadvantage of radiosurgery is that there is a one to three year latency period before obliteration and relief from risk of intracranial bleed occurs. This stands in contrast to embolization and surgery, which immediately eliminate the risk if successful in obliterating or excising the AVM.

From July, 1989, through February, 1996, 130 patients underwent stereotactic radiosurgery at the Toronto-Sunnybrook Regional Cancer Centre (TSRCC). We report the results of the first 50 patients eligible for a minimum of three years' follow-up.

Patient Selection

The radiosurgery group at TSRCC participates in the University of Toronto Brain Vascular Malformation Study Group, a multi-disciplinary group comprised of one radiation oncologist, two interventional neuroradiologists, and three neurosurgeons.

A management algorithm has been developed incorporating radiosurgery, surgery and endovascular therapy or embolization, either singly or in combination.[7] The feasibility of each modality of treatment is assessed by the group. The risk of surgical excision is evaluated with reference to the Spetzler-Martin classification.[8] When feasible, surgery is preferred for patients who have suffered a recent hemorrhage so as to afford immediate protection from further bleeding. When there is sufficient flow through feeding vessels large enough to be cannulated, endovascular treatment is usually recommended as an adjunct. Some lesions are amenable to embolization over several sessions. In every case, complete obliteration of the lesion is required to eliminate further risk of bleeding.[7] Radiosurgery is elected for AVM remnants left after embolization and/or surgery, for lesions unsuitable for embolization and/or surgery or when patient preference dictates. Patients are encouraged to make an informed choice among feasible alternatives.

Twenty women and 30 men underwent radiosurgery. Twenty-four had radiosurgery alone, 17 had embolization prior to radiosurgery, three had surgery prior to radiosurgery and six had radiosurgery subsequent to embolization and surgery. The initial presentation in 26 cases was hemorrhage, 18 presented with seizures, four had headache without obvious hemorrhage and two were discovered incidentally. The patients ranged in age from 16 to 68 years, with a mean age of 37.5 years. Seventeen patients were referred from physicians in the Toronto area and 33 were referred from centres across Canada.

AVM Characteristics

The anatomical distribution of the AVMs was as follows: 14 parietal, 9 temporal, 7 frontal, 2 occipital, 10 basal ganglia/thalamus/internal capsule, 7 corpus callosum and 1 brain stem.

The maximum AVM diameter ranged from 1 to 3 cm except for three AVMs larger than 3 cm in diameter. One roughly spherical AVM measured 3.8 cm in diameter. A second elongated lesion in the corpus callosum measured 5.1 cm in its longest diameter. The third AVM was not appreciated as being larger than 3 cm at the time of therapy, but on follow-up, a small residual which was outside of the initial high dose volume was appreciated.

Method

Treatment process/planning

Patients are admitted on the morning of treatment. The OBT stereotactic frame[9] is applied under local anesthetic. Current patients undergo imaging by digital subtraction angiography (DSA), a dynamic contrast-enhanced CT scan and a magnetic resonance scan. The majority of the initial 50 patients did not have an MRI scan but all had DSA and enhanced CT scanning.

Radiation is administered using the McGill dynamic rotation method described by Podgorsak,[10] using satellite collimators, ranging in size from 1 to 3 cm in 0.25 cm increments. In order to decrease beam on time to 5 minutes on a 6 MV linear accelerator, the beam-flattening filter is removed.[11] Other engineering modifications have been made to enhance treatment efficiency.[12] Forty-seven patients were treated using a single isocentre. Three patients were treated using two isocentres. There has been a trend in our practice toward more frequent use of multiple isocentres. In the last 50 cases, 35 were treated with a single isocentre, whereas 14 were treated with two and one with three.

Following treatment, the patient is monitored overnight in hospital and then discharged the following day.

Dose

Marginal doses vary only to limit the dose to critical normal tissue and do not vary solely with diameter. With the exception of three patients, dose prescriptions were determined by the following: 20 Gy was prescribed to the margin of the AVM nidus provided that critical normal tissue would receive no more than 15 Gy. The isodose at the margin, while usually 90% for 20 Gy, was allowed to vary as long as the above requirements were satisfied. For AVMs situated in or adjacent to critical, eloquent cerebral tissue, 15 Gy was delivered to the margin which was usually encompassed by the 50-70% isodose contour. Marginal doses were 12 Gy for one patient, 15 Gy for 16 patients, 20 Gy for 31 patients and 25 Gy for two patients.

Follow-up

It was intended that patients would undergo annual MRI scans with DSA deferred until either evidence of MRI obliteration or until three years subsequent to treatment had elapsed. Because of patient reluctance and/or difficulties accessing imaging in a timely manner (a result of both geography and health care system access) many patients did not have definitive imaging at two years. Thirty-three patients had MRI scans within 18

months, and 25 patients had MRI scans between 24 - 36 months post treatment. Angiographic follow-up, either confirming obliteration or for assessment at two to three years post-treatment, was available for 39 patients. The time to angiographically confirmed obliteration ranged from 1 year 3 months to 4 years 8 months (the latter mainly due to difficulty organizing the investigation) with a median of 2 years 4 months. In the preparation of this report, out-of-town patients were contacted by phone and asked about general health, seizures, headaches and any focal neurological deficits. When possible, patients were assessed at the University of Toronto Brain Vascular Malformation Study Group Clinic. Other Canadian patients were assessed in their home cities with their imaging studies forwarded to us for review. One patient returned to her native Ecuador and has so far been lost to follow-up. Initially, outcome was to be evaluated at two years but following the observation that some lesions will go on to obliterate between two and three years, we now defer definitive labelling of incomplete obliteration until three years post-treatment.

Results

Fifty patients treated from July 1989 to March 1993 were eligible for a minimum of three years of follow-up, with a range from 3 years to 6 years 8 months, and a median of 4 years 5 months.

Results of therapy (Table 1)

Angiographic documentation of complete obliteration requires absence of the nidus and shunting such as an early draining vein. Partial response means a minimum of 50% reduction in the diameter of the lesion.

Table 1: Results of Radiosurgery.

	No.	%
1. Obliteration Confirmed By Angiography:		
a) complete	25	(50)
b) parenchymal AVM obliterated; residual dural component	2	(4)
2. MRI Evidence of Obliteration (angiography refused)	4	(8)
3. Partial Response at 3 Years:		
a) Early vein only	3	(6)
b) MRI equivocal re: obliteration; angiography pending	1	(2)
c) Residual nidus	9	(18)
4. Hemorrhage		
a) at 18 months; excised	1	(2)
b) at 27 months; fatal	1	(2)
5. No response	1	(2)
6. No Two year follow-up:	3	(6)

Twenty-five patients (50%) had angiographically confirmed obliteration. Two additional patients had evidence of obliteration of the brain parenchymal AVM, but with a dural component remaining. Four patients with MRI evidence of obliteration have refused angiography for confirmation.

Three patients had persistence of an early draining vein only. Two have undergone repeat radiosurgery (at 3 years 8 months and 3 years 1 month post initial treatment). The third patient demonstrated ongoing response at three years such that the minimal remaining shunt may obliterate by four years. A decision about further therapy is deferred until evaluation at four years.

One patient with equivocal MRI findings (suggestive of complete obliteration) is awaiting angiography.

Of nine patients with residual nidus at angiography, three had lesions too large to be completely encompassed in the high dose volume at first treatment. This was recognized at the time of therapy in two patients. One had an elongated lesion with a maximum diameter of 5.1 cm. A small portion of the nidus anterior to the treatment volume recruited new feeders during the three years post treatment. Repeat radiosurgery has been delivered. The second patient with intentional incomplete coverage at first treatment is undecided regarding retreatment. In the third patient, exclusion of part of the nidus was not recognized at the time of first treatment. The three year angiogram showed a small excresence outside the three centimetre high dose volume, with radiosurgery repeated subsequently.

For the remaining six patients with residual nidus, four were identified at three years. One chose surgery, one had repeat radiosurgery and two are undecided. Of two patients with residual nidus demonstrated at two years, one had surgery and the other developed lung cancer, thus declining further imaging.

Two patients hemorrhaged. Both received 20 Gy to the 90% isodose, which encompassed the nidus. One, treated with a 2.5 cm diameter cone, had surgical excision by one of the authors (M.S.) at the time of a severe hemorrhage 18 months post treatment. He had a mild residual hemiparesis but is independent and pursuing job training. Another patient, treated with a 1.0 cm diameter cone, had a definite response on 2 year MRI but suffered a fatal hemorrhage at 27 months post treatment.

One patient had a right thalamic lesion 1.2 cm in diameter. The AVM received a marginal dose of 20 Gy with no response seen at three year angiography. The patient is considering surgical excision.

Three patients have no follow-up out to two years. Two patients were last imaged at 16 and 18 months post treatment, with no and some response respectively. One patient has had no post-treatment imaging of which we are aware, and is lost to follow-up due to her return to her native South America.

Adverse effects

One patient had an acute problem, becoming dysphasic six hours post-treatment. No seizure was witnessed. CT scanning showed no abnormality and she made a complete, spontaneous recovery. At the time of her follow-up angiography, a similar, self-limited event occurred. It is assumed that she suffered a seizure, although none was witnessed.

One patient has a late adverse effect. Prior to radiosurgery, he had three hemorrhages, one partial resection and two partial embolizations resulting in some permanent morbidity. By two years after his first radiosurgery (margin dose: 25 Gy at 90%), he reported difficulty balancing on one foot when taking a shower, but his physical examination was unchanged. He had inadvertent incomplete coverage of his AVM resulting in a small residual outside the initial 3.0 cm high dose volume. At three and one-half years after his first radiosurgery, the therapy was repeated (margin dose: 15 Gy at 67%) for the residual. Beginning one year following the second radiosurgical treatment, he has complained of worsening of his short-term

https://doi.org/10.1017/S0317167100021405 Published online by Cambridge University Press

memory. MR imaging at two years post first treatment showed increased signal in the periventricular aspect of the left atrium of the lateral ventricle, which remained stable one year later, and since has waned. The precise etiology of his decline in short-term memory is unclear. As his AVM is centrally located, the medio-dorsal nuclei of both thalami may have received as much as 25 Gy and 5 Gy, and the columns of the fornix as much as 7.5 Gy and 15 Gy with the first and second treatments respectively.

Dose, diameter and outcome (Table 2)

Although our management evolved to 20 Gy marginal dose preferentially (with 15 Gy marginal dose for those with immediately adjacent critical normal tissue), two patients within our early cohort received 25 Gy. One had angiographically confirmed obliteration.

Table 2: Dose, Diameter and Outcome.

Ratio = # obliterated / total # treated						
Diameter (cm) / **Dose (Gy)**	**< 1.5**	**1.6 - 1.9**	**2.0 - 2.4**	**2.5 - 2.9**	**3.0**	**Total**
12	0	0	0	0	0/1	**0/1**
15	1/3	1/4	1/2	2/5	1/2	**6/16**
20	5/8	2/5	8/10	3/8	0	**18/31**
25	1/1	0	0	0	0/1	**1/2**
Total	**7/12**	**3/9**	**9/12**	**5/13**	**1/4**	

Sixteen patients received 15 Gy marginal dose, with six having angiographically confirmed obliteration. Thirty-one patients received 20 Gy marginal dose, with 18 having angiographically confirmed obliteration. Meaningful analysis of response varying with dose, diameter or combinations is difficult due to small numbers and the different angiographic follow-up across subsets.

Prior therapy and outcome (Table 3)

Prior treatment in general did not increase the angiographically confirmed obliteration rate, with 50% of patients with and 50% of patients without prior treatment having this outcome. Embolization as the only prior treatment resulted in 7/17 angiographically confirmed obliterations, while 1/3 with surgery and 5/6 with surgery and embolization had such documented cures. Again, numbers and angiographic follow-up rates varied across subsets.

Table 3: Prior Treatment and Outcome.

Prior Treatment	# Patients	Angio Oblit	Parenchymal Oblit / Dural Remnant	MRI Oblit
Embolization (E)	17	7	2	1
Surgery (S)	3	1	0	1
E + S	6	5	0	0
None	24	12	0	2
Total	**50**	**25**	**2**	**4**

Discussion

Potential for bias in results

Optimal patient management depends on complete information regarding the efficacy of therapy. All radiosurgery facilities share certain difficulties with respect to complete post-treatment evaluation of patients. Patients may decline to travel great distances for re-examination and imaging or may refuse angiography, preferring a non-invasive MRI scan. A few patients develop life-threatening intercurrent illness and decline further investigation. Nevertheless, epidemiologists and biostatisticians caution that "if more than 20% are lost to follow-up, the results of the study are probably not worth reading."[13] Applying this dictum to the radiosurgery literature, a reviewer has concern that reported results may not be truly indicative of the actual outcome. This concern about incomplete reporting in the radiosurgical literature was underscored by Gaspar's comment regarding its "murkiness".[14]

Many series do not adequately account for the entire cohort eligible for two or three year evaluation. Indeed the commonly employed angiographic obliteration rate calculated by dividing the number of angiographic cures by the number of angiograms performed has the potential to distort the efficacy of therapy, if there are selection biases of patient or physician. For example, many centres recommend angiography only when MRI scanning suggests that obliteration has occurred.[15] As a result, the widely-held benchmark of 80% obliteration is likely incorrect. That 80% obliteration is common to many series suggests that this may simply be the specificity of MRI scan in determining obliteration, as many subjects only undergo angiography after there is an MRI scan compatible with obliteration. We had limited access to magnetic resonance imaging in the early years of this experience. As a result, only 17 patients with MRIs suggestive of obliteration underwent angiography. There were 15 angiographic confirmations of obliteration: a sensitivity rate of 88 per cent.

Efficacy of radiosurgery

The efficacy of radiosurgery for AVMs is poorly documented. Mehta issued a salutary warning about the influence of the "migration of denominators" on reported results.[16] Further, problems with incomplete accounting for all patients makes the determination of the true effect of radiosurgery difficult. Several series will now be reviewed with specific attention to ascertaining the efficacy of treatment, despite the limitations imposed by these methods of reporting.

Recently, Pollock et al. published a report of their experience documenting 134 angiographically proven cures in 313 patients (total of 315 AVMs).[17] Despite all being eligible, angiography was available for only 210 patients (67%) at a minimum of 24 months post treatment. Of these, 134 patients had complete obliteration. He reported a 64% obliteration rate, based on 134 cures in 210 patients having angiography. Unfortunately, the reasons for 103 not undergoing angiography are not disclosed. Yet their outcome can modify this result greatly: if none or all of the 103 have obliterations, then the absolute efficacy of radiosurgery in their series could range from 134/313 (43%) to 237/313 (76%). Given the current information, any claim of a cure rate higher than 43% is strictly theoretical.

Friedman reported on 158 patients but did not specify the number eligible for two year follow-up.[18] Subset analyses using the percentage of angiograms showing complete obliteration over total angiograms performed resulted in reported rates of 69% to 89%, dependent on size. However, examination of the information for the entire cohort (not just the patients undergoing

https://doi.org/10.1017/S0317167100021405 Published online by Cambridge University Press

angiographic follow-up) gives a different perspective. Outcomes are presented only for 85 patients, without explanation for the exclusion of 67. Of the 85 patients, five were lost to and six refused follow-up, and four died of intercurrent disease. For these 85 patients, the outcome can be considered in several ways. First, the uncorrected angiographically confirmed obliteration rate is 48/85 (56%). If one corrects for the fifteen lost to or ineligible for follow-up, then the angiographically confirmed obliteration rate would be 48/70 (69%), varying from 48/85 (56%) to 63/85 (74%) respectively if none or all of the fifteen without follow-up respond. If the four patients with MRI confirmation of obliteration are assumed to all be obliterated, then the obliteration rate might be 48+4/70 (74%) with the potential outcome of those ineligible for follow-up creating a range from 52/85 (61%) to 67/85 (79%).

Colombo reported on 180 patients and cited an 80% obliteration rate at two years.[19] However, there were 79 angiographically confirmed obliterations in 99 patients undergoing angiography, although 120 patients were eligible for two year follow-up. Subsequently, six more showed obliteration at a later follow-up (no data whether these were in the original cohort of 99 having angiography or not). Depending on the denominator used, the obliteration rate could range from 85/99 (85%) to 85/120 (71%). Thus the impact of the fifteen patients without two year follow-up angiography is potentially significant.

Engenhart reported on 212 patients, with 120 patients followed for two years.[20] She presented subset analyses based on volume, with stated results of 50% to 83%. However, if one looks at the cohort of 120 patients with two year follow-up, there were 53 patients with confirmed obliteration out of 97 having angiography. Seven were lost to follow-up and two died of intercurrent problems. The uncorrected obliteration rate is 53/120 (44%). Correcting for lost follow-up, the obliteration rate is 53/111 (48%), but could range from 53/120 (44%) to 62/120 (52%) depending on the outcome of those nine without complete follow-up.

Our results are based on a minimum three year follow-up in forty-five (90%) of our patients, with angiography in thirty-nine (78%). In addition to the 25 patients with no visible AVM remnants on angiography, there are two patients with dural remnants only which are counted as angiographically confirmed successes because the cerebral parenchymal portions were obliterated. One patient has a dural remnant which drains in an anterograde direction without a connection to the brain. The second patient's dural remnant has a cerebral connection. Embolization to obliterate this dural remnant was not technically possible. With follow-ups of 3 years 1 month and 3 years respectively, no adverse events have occurred. With twenty-seven angiographically proven cures of 50 cases treated, our uncorrected obliteration rate of brain AVMs is thus 54 per cent. Three patients did not have two year follow-up, and a further two did not have three year follow-up (now our chronological endpoint in assessing efficacy) due to elective excision at two years in one, and intercurrent disease in the other. Thus, our corrected angiographically confirmed obliteration rate is 27/45 (60%), but could range from 27/50 (54%) to 32/50 (64%), depending upon the outcome of the five without three year follow-up. Further, four had MRI evidence only of obliteration. If all four are presumed cured, then the obliteration rate would be 31/45 (69%), with a range from 31/50 (62%) to 36/50 (72%) given the uncertainties in the outcome of those without three year follow-up.

These reports highlight the difficulties caused by incomplete accounting for all patients in a series. Engenhart[20] had only 6% ineligible for follow-up (lost or inevaluable due to intercurrent disease), while our series had 10%, Colombo[19] 17%, Friedman[18] 18% and Pollock[17] 33%. The range associated with each calculated obliteration rate varied accordingly, with 5% in Engenhart's[20] series; 10% in ours; 14% in Colombo's,[19] 18% in Friedman's,[18] and 33% in Pollock's.[17] These ranges influence the confidence that the calculated obliteration rate is truly indicative of the therapy's efficacy.

Early draining veins

Uncertainty regarding the significance of early draining veins was, in our opinion, resolved by Guo's report of bleeding despite such a minimal residual.[21] While it is unclear how early reports would have classified such an outcome, subsequent reports should characterize them as treatment failures. We recommend further therapy for such patients.

Hemorrhage

Two of our patients suffered hemorrhages, one of them fatal, during the latency period following radiosurgery treatment. It may be that lower radiation doses require longer latency periods before obliteration occurs, during which time the risk of hemorrhage continues unabated. There are too few patients in this series as yet to determine with certainty whether this increased risk exposure is balanced by the lower radiation damage and ischemic complication rate.

Two of this cohort of 50 patients underwent surgical excision of a radiated arteriovenous malformation. Surgery was facilitated by the effects of radiosurgical treatment. There tended to be a gliotic capsule and a firmer consistency to the AVM that facilitated surgical handling, shortening operation time and reducing blood loss.

Adverse effects

Acute adverse effects, usually seizures, have been reported in 4.6% by Friedman,[18] 3.5% by Lunsford[22] and 1.6% by Coffey.[23] Our series with 1 of 50 patients (2%) having an acute adverse reaction, which was likely a seizure, is in keeping with the experience of others.

Late adverse effects, that is, neurological deficits, have been reported in 11.6% by Engenhart with 7.3% recovering completely.[20] Friedman reported a 1.3% permanent complication rate.[18] Our series, with one patient (2%) having a permanent complication, is at the lower end of the reported spectrum. This may be due to our lower marginal dose (15 Gy to eloquent tissue).

Precise dose-tolerance curves for normal brain cannot be constructed yet from the collective experience. Normal tissue tolerance may be especially difficult to determine given the following three factors: low incidence of complications; challenges in determining the site (and dose) of injury; the likely interrelated factors of dose to and volume of eloquent tissue treated plus the influence of hemorrhage or therapy prior to radiosurgery. Our one patient, with multiple previous hemorrhages, operation and embolizations had morbidity prior to radiosurgery reflective of reduced normal tissue tolerance. While the exact location of his deficit is not apparent, total doses (over two treatments separated by 3.5 years) to the medio-dorsal nuclei and

columns of the fornix were perhaps as much as 32.5 Gy and 20 Gy respectively.

Dose

The optimal dose for AVM obliteration is still poorly defined. It will ultimately reflect a balance between the rates of inducing obliteration vs. complications. Its determination is confounded by three factors. First, to minimize dose to normal brain, it is common for centres to decrease the marginal radiation dose as the AVM size increases. Secondly, the impact of dose homogeneity across the high-dose volume is undetermined, with margin isodoses often ranging from 50% to 90% between series. Finally, the afore-mentioned problems in interpreting results based on "migration of denominators" and incomplete follow-up make it difficult to determine the true efficacy of the doses used.

Engenhart established the threshold dose as 15 Gy (no obliterations in 13 patients treated to 14 Gy) and noted a greater response with increasing dose (50% obliteration with 15 Gy vs. 80% with 20 Gy).[20] Colombo reported that the only significant variable with respect to obliteration was the peripheral dose.[19] Unfortunately, these doses are not explicitly stated. Furthermore, he describes his practice of reducing the marginal dose with increasing AVM volume so that the effect of one factor independent of the other is likely inextricable.

We used two doses, 15 or 20 Gy, regardless of volume provided eloquent tissue received no more than 15 Gy. We too noted a trend towards a higher obliteration rate with 20 Gy. Of thirty-one treated to a margin dose of 20 Gy, twenty-four had angiography with eighteen confirmed obliterations. Of sixteen treated to a margin dose of 15 Gy, twelve had angiography with six confirmed obliterations. Finally, we observed the following with interest: one 3 cm lesion, treated to 15 Gy at the margin (67% isodose), was angiographically confirmed to be obliterated. One lesion < 1. 5 cm did not respond to a margin dose of 20 Gy (90% isodose). Despite a comparable maximum dose, higher marginal dose and smaller volume, the latter failed to show any radiation response. The precise relationship between margin dose, maximum dose and obliteration rate is likely complex and influenced by other factors as well.

Despite these considerations, we must evaluate the available data. We have shown a 54% uncorrected and a 60% corrected (for those without follow-up) angiographically confirmed obliteration rate. Engenhart's series, with the strength of an even lower "lost to follow-up" factor than ours, has uncorrected and corrected angiographically confirmed obliteration rates of 44% and 48% respectively.[20] Given that the doses in the two series were likely of a similar range, these results are perhaps indicative of the rates using 15 to 20 Gy. Although Colombo has not specified his peripheral doses to allow comparison with others, they are likely higher and thus may account for an uncorrected angiographically confirmed rate of 71%.[19]

One cannot draw firm conclusions about dose from our data or much of the literature. Although we have demonstrated response with 15 Gy margin dose, the low morbidity and trend toward a higher obliteration rate with 20 Gy has prompted us to select this dose in preference. Nevertheless, if the immediately adjacent tissue is eloquent, we still restrict the dose to 15 Gy.

Volume

While larger AVM volumes are thought to be associated with lower obliteration rates, this influence may be difficult to isolate, as noted above, given the small numbers reported in many series, plus the concomitant inverse variation in dose with size in many series. Interestingly, Colombo's report shows a striking difference in obliteration rates with different volumes, yet he states that only the marginal dose correlated significantly with outcome.[19] Sebag-Montefiore reported on patients all treated with 17.5 Gy to the margin, regardless of volume.[24] Of 64 patients followed for at least two years, 52 had angiography. Of these, 25 of 33 lesions < 10 cc obliterated compared with 9 of 19 lesions > 10 cc. Overlying feeding arteries and draining veins can obscure nidus definition and thus contribute to inter-observer variation. Given this arbitrariness of dichomotization (< 2 cm, > 2 cm), plus the sample size and lack of complete angiographic follow-up, there is no evidence from our data of differential outcome based on lesion size.

Prior treatment

While our sample size and lack of complete angiographically follow-up preclude firm conclusions about the effect of prior treatment on obliteration, embolization and surgery often reduced the size of the lesion to one approachable by radiosurgery.

This series with 90% three year follow-up (78% angiographic) is uncommon in its extent of follow-up, complete accounting of all patients, and stated method of determining the denominator. A review of the literature underscores the difficulties in ascertaining the obliteration rate. The confidence with which data can be interpreted as accurately reflecting the efficacy of therapy is critically influenced by the completeness of accounting for the entire cohort. Thus, substantive evidence of obliteration rates of 80% or greater is lacking.

Our uncorrected and corrected (for those without three year follow-up) angiographically confirmed obliteration rates are 54% and 60% respectively. Our results could rise to 72% if all the MRI "cures" and those without three year follow-up are angiographically confirmed as obliterations. Nevertheless, our results are lower than most stated in other published series. Given the magnitude of our follow-up, our data may be quite reflective of the efficacy of using 15 Gy and 20 Gy marginal dose. With the selection inherent in our multidisciplinary group's management algorithm, our radiosurgery population may even be an optimum one. If so, results from other groups with their own algorithms will likely differ and could even be lower for comparable doses. To the extent that obliteration is influenced by marginal dose (Colombo[19] found that to be the only independent prognostic factor), results may vary depending on doses used.

To advance our collective knowledge, and enhance patient management, determination of the efficacy of radiosurgery for AVMs is essential. This will be known only through complete reporting from all centres, including standard methods of describing the dose prescription and results to allow comparison between series.

Such information will also aid our understanding of prognostic factors. These likely include patient, lesion and treatment characteristics. Currently, the data do not allow conclusions to be drawn. With sufficient reporting, meta-analysis may allow the

the independent and inter-dependent influences of these factors to be better delineated as predictors of response.

Finally, follow-up is necessary beyond the time to determine the efficacy of treatment in terms of obliteration. Only such extended follow-up will provide data regarding long-term effects including second malignancy.

ACKNOWLEDGEMENTS

The authors thank Dr. Philip Porter, Dr. M. Christopher Wallace and Ms. Edmee Franssen for their support and assistance in preparing this manuscript.

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