ORIGINAL ARTICLE

Factors Predictive of Obliteration After Arteriovenous Malformation Radiosurgery

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ABSTRACT: *Objective:* To investigate predictive factors of complete obliteration following treatment with linac-based stereotactic radiosurgery for intracerebral arteriovenous malformations. *Methods:* Archived plans for 48 patients treated at the British Columbia Cancer Agency and who underwent post-treatment digital subtraction angiography to assess obliteration were studied. Actuarial estimates of obliteration were calculated using the Kaplan-Meier method. Univariate and multivariate Cox proportional hazards models were used for analysis of incidence of obliteration. Log-rank test was used to search for parameters associated with obliteration. *Results:* Complete nidus obliteration was achieved in 38/48 patients (79.2%). Actuarial rate of obliteration was 75.9% at 4 years (95% confidence interval 63.1%-88.6%). On univariate analysis, prescribed dose to the margin (p=0.002) and dose to isocentre (p=0.022) showed statistical significance. No parameters were significant in a multivariate model. According to the log-rank test, prescribed dose to the margin of >20 Gy (p=0.004) and dose to the isocentre of >25 Gy (p=0.004) were associated with obliteration. *Conclusion:* Reported series in the literature suggest a number of different factors are predictive of complete obliteration of arteriovenous malformations following radiosurgery. However, differing definitions of volume and complete obliteration makes direct comparison between series difficult. This study demonstrates that complete obliteration of the nidus following linear accelerator-based stereotactic radiosurgery for arteriovenous malformations appears to be most closely related to the prescribed marginal dose. In particular, a marginal dose of >20Gy is strongly associated with obtaining complete obliteration of the nidus.

RÉSUMÉ: Facteurs de prédiction de l'oblitération par la radio chirurgie de malformations artérioveineuses. *Objectif :* Le but de l'étude était de déterminer quels sont les facteurs de prédiction d'une oblitération complète de malformations artérioveineuses intracérébrales suite au traitement par radio chirurgie stéréotaxique par Linac. *Méthodes :* Nous avons étudié le plan de traitement de 48 patients, qui ont subi une angiographie de soustraction numérique après traitement au British Columbia Cancer Agency, pour évaluer l'oblitération. L'estimation actuarielle de l'oblitération a été calculée au moyen de la méthode de Kaplan-Meier. Nous avons utilisé le modèle de régression univarié et multivarié des risques proportionnés de Cox pour analyser l'incidence de l'oblitération. Le test de rang a été utilisé pour identifier les paramètres associés à l'oblitération. *Résultats :* L'oblitération complète du foyer morbide a été réalisée chez 38 des 48 patients (79,2%). Le taux actuariel d'oblitération était de 75,9% après 4 ans (intervalle de confiance à 95% de 63,1% à 88,6%). À l'analyse univariée, la dose prescrite en périphérie (p = 0,002) et la dose à l'isocentre (p = 0,022) étaient significatives au point de vue statistique. Aucun paramètre n'était significatif à l'analyse multivariée. Au test de rang, la dose de > 20 Gy (p = 0,004) en périphérie et la dose de > 25 Gy (p = 0,004) à l'isocentre étaient associées à l'oblitération. *Conclusion :* Les séries de patients rapportées dans la littérature suggèrent différents facteurs de prédiction de l'oblitération complète des MAV par radio chirurgie. Cependant, des définitions différentes du volume de la MAV et de son oblitération complète rendent difficile la comparaison directe entre les séries. Cette étude démontre qu'une oblitération complète du foyer morbide d'une MAV après traitement par radio chirurgie stéréotaxique semble être étroitement reliée à la dose marginale prescrite. Une dose marginale de > 20 Gy est fortement associée à une oblitération complète du foyer morbide.

Intracranial arteriovenous malformations (AVMs) are congenital lesions consisting of focal areas of abnormal dilated arteries and veins within the brain parenchyma. Small arterioles within the AVM have an absent smooth muscle layer and lack a capillary bed[1]. This results in arteriovenous shunting through one or more fistulae. This direct shunting leads to a risk of venous rupture due to the high pressures involved with potentially devastating consequences[2]. The prevalence of intracranial arteriovenous malformation in the general population is estimated to be anywhere between 0.001% and 0.52%[3-6]. Typically patients present following an intracerebral haemorrhage (42-72%), most commonly between the ages of 20 and 40 years[3,7-10]. Other presenting symptoms include seizures,

consequences of mass effect and isolated headache[2]. However, with modern imaging techniques we are seeing an increasing number of patients with asymptomatic arteriovenous malformations.

Treatment options for AVMs include surgery, embolization, stereotactic radiosurgery (SRS) or a combination of these modalities. Although there are no randomised trials to aid decision making, the American Stroke Association has published recommendations[11]. These are largely based on the Spetzler-Martin grading scale[12], a simple system devised to predict the risk of morbidity and mortality following neurosurgery for AVMs. Lesions are graded on the basis of size, pattern of venous drainage and neurological eloquence of adjacent brain. Radiosurgery is generally recommended for lesions in anatomical locations that may be associated with an increased risk of surgical complications. This is particularly the case for AVMs in eloquent regions of the brain, owing to their anatomic location or feeding-vessel anatomy, where surgical resection is likely to result in neurologic deficits. The goal of SRS is to induce complete luminal obliteration thereby preventing future haemorrhage. Initial studies demonstrated the effectiveness of Gamma Knife SRS[13-14]. Subsequently, linear accelerator-based treatment has been shown to be equally effective[15-19].

The British Columbia Cancer Agency (BCCA) has been treating intracerebral AVMs using single-fraction linear accelerator-based SRS since 1997. Patients with intracranial AVMs who may be candidates for SRS are reviewed by a multi-disciplinary group. This group is comprised of radiation oncologists, neurosurgeons, and a neuroradiologist who make up the precision radiotherapy team at BCCA. The feasibility of each treatment modality is discussed, and management recommendations are made by the group. Typically, SRS is recommended for lesions unsuitable for embolization and/or surgery or for residual AVMs after unsuccessful embolization and/or surgery. The aim of this study was to investigate factors predictive of complete nidus obliteration following treatment with linear accelerator-based SRS.

MATERIALS AND METHODS

Between 25th September 1997 and 20th July 2006, 79 patients were treated with linear accelerator-based radiosurgery for intracerebral AVM. The cut-off date was selected to allow a minimum of four years follow-up. Fifty-six patients underwent digital subtraction angiography (DSA) to assess nidus obliteration following treatment. Of the 23 patients who did not undergo DSA, 19 had assessment by magnetic resonance imaging (MRI) alone, two were lost to follow-up, one required emergency surgery following a bleed post-SRS, and one died of an unrelated cause within three years of treatment. Archived plans were available for assessment in 52 out of the 56 patients who underwent DSA. A further four patients who had had prior treatment with either SRS or proton therapy were also excluded from analysis, leaving 48 patients for assessment. The study was approved by the institutional ethics committee.

Radiosurgery technique

All patients underwent digital subtraction angiography as well as an MRI scan prior to treatment. Patients were treated using an invasive stereotactic head frame (BrainLAB AG, Heimstetten, Germany) for use in performing the planning computed tomography (CT) scan and for radiosurgery. Target localization and definition of a reference coordinate system were provided by a stereotactic localizer box (BrainLAB AG, Heimstetten, Germany). Planning CT scans were done on a GE Lightspeed RT16 scanner (GE Healthcare Inc., WI) with an axial image slice thickness of 1.25 mm. The CT images were fused to both a digital subtraction angiogram and an axial PD-weighted MRI for anatomy and target delineation. The AVM nidus was contoured as the gross target volume. A 1.0 mm 3-dimensional margin around the contoured AVM was used for the planning target volume (PTV).

Treatment planning was performed using the BrainSCAN SRS treatment planning system (BrainLAB AG, Heimstetten, Germany). Prior to August 2000, plans consisted of multiple arcs using circular, cone-shaped collimators and 1-4 isocentres (n = 31). The median number of arcs was 8 (range, 4-16). After this date, most treatments were planned with non-coplanar static conformal fields using a Micro MLC (μMLC) (BrainLAB AG, Heimstetten, Germany) and a single isocentre (n=17). The median number of fields using this approach was 5 (range, 4-18). Plans were normalized to 100% at the isocentre. An isodose contour conforming to the PTV was selected as the prescription isodose. For plans using multiple arcs, prescription was either to the 50% (n=12) or to the 80% isodose volume conforming to the PTV. In one case, prescription was to the 65% isodose. For plans using multiple static conformal fields, prescription was to the 80% isodose volume conforming to the PTV. Prescription to the 50% isodose was used for the majority of patients treated until 1999, followed by a transition period when this prescription was used only occasionally. No patients treated since September 2001 had dose prescribed to the 50% isodose. Treatment was delivered using 6 MV photons on a Varian CL21 EX linear accelerator (Varian Medical Systems Inc., Palo Alto, CA).

Dose prescription

The prescription dose was at the discretion of the treating physician and varied depending on AVM size, location and patient age. The median prescription dose to the PTV was 20 Gy (range, 12-25 Gy). The median dose to isocentre was 31.25 Gy (range 15-50 Gy). Forty-seven patients (97.9%) were prescribed at least 16 Gy to the periphery of the PTV. One patient was prescribed 12 Gy: an AVM in the deep parietal lobe of a 21 year-old patient. The mean total dose for all patients was 29.8 ± 7.5 Gy at the isocentre.

Follow-up evaluation

All patients were scheduled for clinical follow-up after treatment. Routine follow-up involved annual MRI scans with digital subtraction angiogram deferred until MRI evidence of complete obliteration or until three to four years after treatment. Median time from treatment to angiogram was 29.8 months (range 12-68 months). Complete angiographic obliteration was defined as normal blood flow, absence of pathologic vessels at the site of the nidus, and normalization of flow in the draining veins.

Statistical analysis

Actuarial estimates of complete nidus obliteration were calculated using the Kaplan-Meier method[20]. Univariate and multivariate Cox proportional hazards models were used for analysis of complete obliteration. The following variables were examined in the univariate analysis: age, lesion location, Spetzler-Martin grade, lesion volume, lesion diameter (largest dimension), prescribed dose to the margin, and dose to the

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Table 1: Pre-treatment patient and AVM characteristics (n=48)

Age (years)		Median 37 (range 10-72)
Sex	Male	21 (43.8%)
	Female	27 (56.3%)
ECOG performance status	0	18 (37.5%)
	1	21 (43.8%)
	2	8 (16.7%)
	3	0
	4	1 (2.1%)
Smoker (n=32)		12 (37.5%)
Diabetes (n=36)		1 (2.8%)
Hypertension (n=36)		6 (16.7%)
Symptoms prior to SRS	bleeding	29 (60.4%)
	seizures	13 (27.1%)
	headache	4 (8.3%)
	incidental finding	2 (4.2%)
Extranidal aneurysm		5 (10.4%)
Spetzler-Martin grade (n=43)	1	1 (2.3%)
	2	10 (23.3%)
	3	25 (58.1%)
	4	7 (16.3%)
Lesion diameter (mm)		Median 23.6 (range 9.9-53.4)
Lesion volume (cc)		Median 2.5 (range 0.3-21.2)
AVM location	deep	10 (20.8%)
	other	38 (79.2%)
Prior treatment	surgery	1 (2.1%)
	embolization	14 (29.2%)
	surgery + embolization	1 (2.1%)
	embolization + carotid ligation	1 (2.1%)

Notes: "deep" location = basal ganglia, thalamus, brain stem; "other" location = frontal, parietal, temporal, occipital, intraventricular, cerebellar, corpus callosum (from Wegener et al[21]. Spetzler-Martin grade correlates with surgical outcome[12]. Partial data only was available for Spetzler-Martin grade, smokers, and prevalence of hypertension and diabetes mellitus.

isocentre. Log-rank test was used to search for dosimetric parameters associated with obliteration. The patient cohort was divided into two subgroups according to the value of the parameter. For continuous variables cut-off values were introduced in an incremental fashion. For example, if the parameter under consideration was lesion volume and a current cut-off value was 10 cc, group one comprised patients whose lesion volume was >10 cc and group two ≤10 cc. The difference in obliteration rates in these two groups was examined for statistical significance using log-rank test, and parameter values leading to $p<0.05$ were recorded. Full ranges of values of the following dosimetric parameters were explored: lesion volume, lesion diameter, dose prescribed to the margin, and dose to the isocentre. Dose to the margin/lesion volume combinations were also tested for their association with obliteration rates using the log-rank test. In this analysis one subgroup comprised patients receiving a certain dose or larger and having lesion volume of certain size or smaller. The other subgroup comprised patients who had at least one of these conditions not fulfilled. Statistical analyses were undertaken using Statistica (Statsoft, Tulsa, OK).

RESULTS

Pre-treatment patient characteristics are shown in Table 1. The anatomic locations of the AVMs were as follows: four frontal, eight parietal, ten temporal, seven occipital, seven cerebellar, one ventricular, and one corpus callosum. There were ten patients with an AVM in a "deep" location. Deep locations

included basal ganglia (1), thalamus (6), and brainstem (3). The most common presenting symptom was intracerebral haemorrhage (60.4%). Seventeen patients (35.4%) had been previously treated either by surgery or embolization or a combination of these modalities. Median follow-up was 41 months (range 24-139 months).

Thirty-eight patients (79.2%) had complete obliteration of the AVM nidus on angiogram following treatment. Kaplan-Meier actuarial complete obliteration rate was 75.9% (95% confidence interval 63.1%-88.6%) at four years. The Kaplan-Meier curve for proportion of patients failing to achieve complete obliteration is shown in Figure 1. For plans prescribed to the 50% isodose, the crude rate of obliteration was 75% and for plans prescribed to the 80% isodose, 80.0%. There were insufficient patients, however, treated to the 50% isodose (n=12) to perform statistical analysis.

Table 2 shows the results of the univariate and multivariate analyses. When the parameters in Column 1 were entered into the Cox proportional hazards model one at a time, prescribed dose to the margin and the dose to the isocentre showed statistical significance. Lesion volume and diameter did not show statistical significance. In a multivariate analysis, none of the parameters were statistically significant.

Figure 2 shows the distribution of obliterated and non-obliterated AVMs according to prescribed dose and both lesion diameter and lesion volume. The AVMs that failed to obliterate
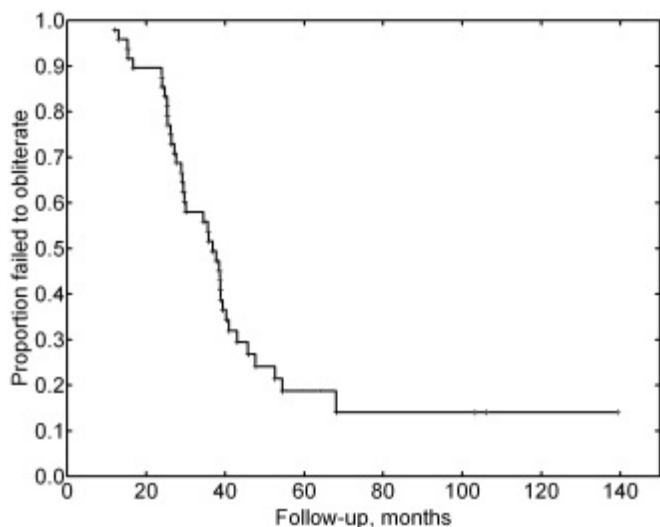
Figure 1: Actuarial proportion of patients who failed to obliterate.

Figure 2: Outcomes following treatment according to prescribed marginal dose, lesion diameter and lesion volume.

following treatment were generally associated with lower marginal doses and greater lesion diameters and volumes.

Table 3 shows the results of searching for cut-off values using the log-rank test. Prescribed dose to the margin (p=0.004), and dose to the isocentre (p=0.004) were associated with an increased incidence of complete nidus obliteration. Lesion volume was only marginally significant (p=0.048). According to the log-rank test, the cut-off value for prescribed dose was >20 Gy, for dose to the isocentre >25 Gy, and for lesion volume >6.4 cc. The Kaplan-Meier curves of complete obliteration for prescribed dose to the margin ≤20 Gy and >20 Gy are shown in Figure 3.

The log-rank test was also performed for a variety of prescription dose/lesion volume combinations. The strongest association was found for prescription dose equal to or larger than 20 Gy and lesion volume of 10 cc or less, with an actuarial rate of obliteration of 91.6%. If one of these conditions was not met, the obliteration rate was 60.9% (p=0.033).

DISCUSSION

The results from this series of 48 patients treated for AVMs with linear accelerator-based SRS are consistent with other series
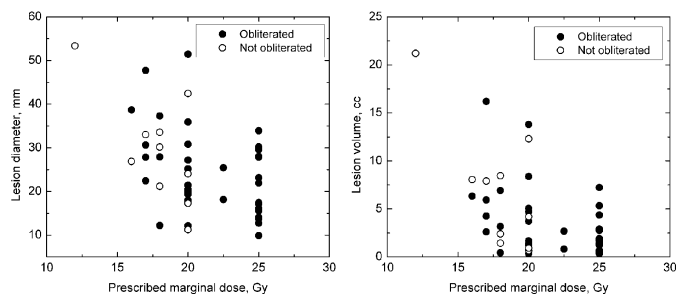
reported in the literature which suggest complete nidus obliteration in 60-90% of patients[15,22-26]. The AVMs were initially treated with Gamma Knife radiosurgery[13]. Lunsford et al[14] published a complete obliteration rate of 80% at two years in 46 patients undergoing Gamma Knife radiosurgery. Flickinger et al[25] demonstrated a complete obliteration rate of 72% with three year angiographic follow-up in 197 patients. Meanwhile, Pollock et al[27] reported on their four year experience in 65 patients with AVMs using SRS for smaller lesions (<3cm diameter) and Spetzler-Martin grades 1 and 2. The mean dose to the periphery of the AVM nidus was 21Gy. They reported an 84% complete obliteration rate based on 27 out of 32 patients who had post-treatment angiography with a minimum of two years of follow-up.

Subsequently, a number of institutions have reported obliteration rates following linear accelerator-based radiosurgery[15-19,26]. Zabel et al[18] treated 110 patients with linear accelerator-based radiosurgery. The actuarial complete obliteration rate was 67% after four years. Young et al[26] reported an angiographically confirmed obliteration rate of 60% in a series of 50 patients.

Whilst there are no randomised controlled trials comparing obliteration rates with either Gamma Knife or linear accelerator-based treatment, Orio et al[28] assessed treatment outcome in 96 patients treated with linear accelerator-based SRS and 91 patients treated with Gamma Knife SRS at the same institution.

Table 2: Results of statistical analysis using Cox proportional hazards

Parameter	Cox proportional hazards, univariate, p value	Cox proportional hazards, multivariate, p value
Age	0.126	0.714
Spetzler-Martin grade	0.224	0.864
Previous embolization	0.293	0.891
Location	0.466	0.779
Prescribed dose	0.002	0.099
Dose to isocentre	0.022	0.586
Lesion diameter	0.449	0.079
Lesion volume	0.091	0.067

Table 3: Results of testing parameters for association with failure to obliterate

Parameter	Log-rank test, p	Cut-off value	Actuarial rate of obliteration, %
Location	0.458	N/A	N/A
Spetzler Martin grade, 1/2 vs. 3/4	0.810	N/A	N/A
Previous embolization	0.295	N/A	N/A
Prescribed dose, Gy	0.004	>20 Gy	100
		≤20 Gy	77.5
Dose to isocentre, Gy	0.004	>25 Gy	91.7
		≤25 Gy	78.2
Lesion diameter	N/S	N/A	N/A
Lesion volume*	0.048	>6.4 cc	61.9
		≤6.4 cc	90.1

Notes: N/S - not significant; N/A - not applicable. * While log-rank test resulted in a p-value of 0.048, it should be noted that only 10 patients were in the group with lesion volume > 6.4 cc.

The estimated complete obliteration rate at five years was 66% overall with obliteration rates of 60% in the linear accelerator group and 72% in the group treated with Gamma Knife. The difference was not statistically significant (p=0.97). Late toxicity occurred in 8% of patients in both groups (p=0.61). Post treatment haemorrhage in the latent period between treatment and obliteration, however, occurred in 13% of the gamma knife group and 6.2% of the linac-based treatment group (p=0.05).

Various studies have attempted to assess predictors of complete obliteration following SRS. The strongest predictor of obliteration in our series was dose to the margin (p=0.002 on univariate analysis) with patients prescribed >20Gy significantly more likely to achieve complete obliteration (p=0.004 log-rank test). This finding is in keeping with Flickinger et al[25] who assessed the relationship of dose and volume to obliteration. Multivariate logistic regression analysis of 197 patients who had undergone treatment with Gamma Knife revealed a significant independent correlation with minimum dose (p=0.04). On the other hand, they found no evidence of a correlation with either volume or maximum dose which contrasts with our own findings. Log-rank test demonstrated a significantly lower rate of obliteration for lesions >6.4cc (p=0.048). However, numbers were small at this cut point and, consequently, this result may be unreliable.

Of note, we found no evidence that lesion location was a predictor of obliteration on univariate analysis (p=0.385). This is in contrast to the findings of Zabel et al[18] who demonstrated an association between obliteration rates and location on univariate analysis (p<0.004), although not on multivariate analysis. However, it is important to note that lesion location also correlated with prescribed dose, with lower doses being applied to lesions in eloquent areas. It is, therefore, possible that this finding was simply a function of marginal dose as outlined above.

Furthermore, we found no evidence that either Spetzler-Martin grade or a previous history of embolization was associated with obliteration rates. The Spetzler-Martin grading scale was initially devised as a means of predicting morbidity and mortality following surgical resection of AVMs and, whilst the scale has been validated by a number of surgical centres as a reliable predictor of microsurgical outcomes[29-31], its use as a predictor of outcome following SRS remains controversial. A number of studies have demonstrated correlation with outcome post-SRS[18,19]. Zabel et al[18] found that Spetzler-Martin grade 1/2 vs. 3/4 was the only variable to predict for obliteration on both univariate and multivariate analysis. However, no correlation was evident in the large series of 220 patients treated by Gamma knife assessed by Pollock et al[32]. Meanwhile, Schlienger et al[33], reporting results from 169 patients treated with linear accelerator-based SRS, found that absence of prior embolization was an independent factor on multivariate analysis predicting successful treatment.

One limitation of our study is that only 48 patients out of a total of 79 treated were available for analysis. The majority of patients lost to analysis were excluded because they did not
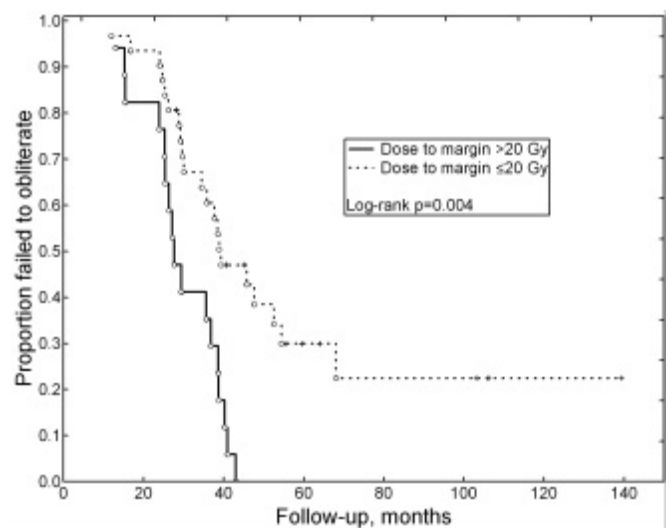

Figure 3: *Actuarial proportion failed to obliterate according to prescribed dose to margin ≤ or >20 Gy.*

undergo post-treatment digital subtraction angiography. This is considered the gold standard approach for the assessment of nidus obliteration with a specificity of 100%, compared to only 80% for MRI[25]. Whilst there is no reason to believe that there is any difference between those who underwent angiography and those that did not, it is possible that unanticipated factors could have led to an imbalance between the groups. Furthermore, although we found no evidence that lesion location, Spetzler-Martin grade, and previous history of embolization were associated with obliteration, it may simply be that our sample size was too small to detect an effect.

CONCLUSION

The various reported series in the literature suggest a number of different factors are predictive of complete obliteration of AVMs following radiosurgery. However, differing definitions of volume and complete obliteration makes direct comparison between these series difficult. This study demonstrates that complete obliteration of the nidus following linear accelerator-based stereotactic radiosurgery for AVMs appears to be most closely related to the prescribed marginal dose. In particular, a marginal dose of >20Gy is strongly associated with obtaining complete obliteration of the AVM nidus.

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