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An analysis of the dose–response for arteriovenous malformation radiosurgery and other factors affecting obliteration ☆

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Abstract

Purpose: The aim of this study was to better understand arteriovenous malformation (AVM) obliteration rates after radiosurgery.

Methods and materials: We studied obliteration after Gamma knife radiosurgery in 351 AVM patients with 3–11 years of follow-up imaging. The median marginal dose was 20 Gy (range: 12–30) and median treatment volume was 5.7 cm^3 (range: 0.26–24). Stereotactic targeting was with angiography alone in 250 AVMs, and additional magnetic resonance (MR) imaging in 101 AVMs.

Results: We documented obliteration by angiography in 193/264 (73%) AVM, and by MR alone in 75/87 (86%) AVM for a 75% corrected obliteration rate. We identified persistent out-of-field nidus in 18% of embolized vs. 5% of non-embolized patients, ($P = 0.006$). Multivariate analysis correlated in-field obliteration with marginal dose ($P < 0.0001$) and sex ($P \leq 0.026$, but not for overall obliteration $P = 0.19$). A mathematical dose–response model for overall obliteration was constructed to generate a dose–response curve for AVM obliteration with a maximum overall obliteration rate of 88% and minimal improvement above 25 Gy. We could not define the value of α/β for AVM obliteration to a level of statistical significance.

Conclusion: The rate of AVM obliteration from radiosurgery depends on the marginal dose administered with a dose–response curve that reaches a maximum of approximately 88%. The dose–response plateau reflects problems with target definition which is made more difficult by prior embolization.

Keywords: Radiosurgery; Stereotactic; Arteriovenous malformation; Linear–quadratic; Radiobiology

1. Introduction

Stereotactic radiosurgery is an alternative to resection of intracranial arteriovenous malformations (AVM) that has been remarkably successful in eliminating the lifelong threat of intracranial hemorrhage [5,6,9–11,13–15,17,19,20,25,29,32]. Pathological changes after AVM radiosurgery have been well described [4,26,28,30]. The initial effect of high-dose single fraction radiation on AVMs appears to be through damage to endothelial cells. Subsequently, the intimal layer progressively thickens via proliferation of myofibroblasts that elaborate an extracellular matrix including type IV collagen. Late changes observed include cellular degeneration, hyaline transformation, fragmentation of the elastic laminae and mineralization in vessel walls. This histopathological response to high-dose irradiation leads to progressive stenosis, luminal closure, and eventual obliteration of the AVM nidus.

Overall obliteration rates vary in most series between 60 and 90% [5,6,9–11,13–15,17,19,20,25,29,32]. The most important factors that have been associated with AVM obliteration after radiosurgery are minimum dose to the AVM nidus (marginal dose) and AVM volume [9,10,13,14,20,32]. Post-radiosurgery complications (usually temporary) occur in approximately 9% of patients, vary with location and dose, and are extensively discussed elsewhere [7,8]. It can be difficult to separate the effects of dose and volume on obliteration since most centers prescribe lower doses for larger AVMs in order to reduce complications. The causes of failure to obliterate an AVM after radiosurgery include insufficient dose (which is sometimes reduced to limit complications for large-volume or deep-seated AVMs) and various reasons for finding portions of AVM nidus outside the treatment isodose volume [10,20,25,26]. Persis-

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tent out-of-field nidus can result from recanalization of uniradiated portions of nidus that were temporarily occluded by embolization or hemorrhage and from difficulty in defining the entire nidus at treatment [10,20,25,26]. The probability of obliterating an AVM after radiosurgery, *P*(overall obliteration), therefore depends on the probability of identifying patent untargeted nidus at 3-year follow-up, *P*(miss), and the probability of obliterating nidus within the treatment volume, *P*(in-field obliteration), according to the following formula:

$$P(\text{overall obliteration}) = [1 - P(\text{miss})] \times P(\text{in-field obliteration}) \quad (1)$$

In this report, we endeavor to better understand factors affecting ultimate radiosurgical AVM obliteration. This is best done through separate analyses of the probability of finding untargeted patent nidus at 3-year follow-up, *P*(miss), and the probability of in-field nidus obliteration, which represents the true radiobiological response of the AVM. We hypothesized that the radiobiological response of AVM (in-field obliteration) would primarily depend on radiation dose and could be described by a linear–quadratic expression of marginal dose (minimum nidus dose). We also hypothesized that the probability of finding untargeted residual AVM would increase with a history of prior embolization, prior hemorrhage, increasing treatment volume, and would decrease with adding stereotactic MR to angiographic imaging [2,3,18,20–22,24].

2. Methods and materials

At the University of Pittsburgh, 351 patients who underwent Gamma Knife radiosurgery in a 10-year interval between 1987 and 1997, and completed 3-year follow-up imaging were eligible for this study. We excluded repeat radiosurgery procedures for prior unsuccessful photon or proton beam radiosurgery and patients with large AVMs who underwent prospectively planned staged radiosurgery (where only one-half to one-third of the nidus was irradiated at each of two or three treatment sessions 4–6 months apart). All patients gave informed consent to participate in this retrospective study, which was approved by the University of Pittsburgh Institutional Review Board. The median follow-up was 51 months (range: 36–127 months).

2.1. Patient/AVM characteristics and prior treatment

The median patient age was 34 years (range: 2–76); 165 patients were males and 186 were females. The Spetzler–Martin AVM grades were: 12 patients with Grade 1, 100 with Grade 2, 159 with Grade 3, 31 with Grade 4, and 49 with Grade 6 [27]. Prior to radiosurgery, 147 patients' AVMs had bled (136 once, 22 twice, 10 three times, and three AVM bled five times). There were 38 patients who underwent attempted surgical resection prior to surgery (31 with one operation, four with two operations, two with three operations, and one with four operations). Prior embolizations were performed in 48 patients (once in 25, twice in 17, and three to six times in six patients).

2.2. Radiosurgery and treatment planning details

Stereotactic targeting was performed with angiography alone for 250 AVM, and with angiography plus stereotactic magnetic resonance (MR) imaging for 101 AVM. Treatment volumes determined using computer dose-planning volumetric software varied from 0.26 to 24 cm^3 with a median of 5.7 cm^3. Minimum doses prescribed to the AVM nidus (marginal doses) varied from 12 to 30 Gy with a median of 20 Gy. Only one patient received a marginal dose greater than 26 Gy (30 Gy prescribed to the 80% isodose volume). Maximum doses (D_{max}) varied from 22.2 to 50 Gy with a median of 40 Gy. The median treatment isodose was 50%, with a range from 40 to 90% (40% in three, 50% in 212, 55–65% in 56, 70% in 41, 80% in 22, and 90% in 12 patients).

2.3. Statistical analysis

Stepwise forward-conditional multivariate logistic regression analyses of in-field obliteration and the probability of finding out-of-field persistent nidus were performed using SPSS software. Alpha/beta ratios (α/β) were calculated with several methods. Approximate α/β ratios were calculated from the regression coefficients for marginal dose and square of marginal dose from logistic models. The formula for multivariate logistic regression modeling of variables (a, b, c, …) is:

$$P = e^R/(1 - e^R), \quad \text{with } R = [C + r_a(a) + r_b(b) + r_c(c) + \cdots, \quad (2)$$

where C is a constant and ($r_a + r_b + r_c + \cdots$) are the respective regression coefficients for variables (a, b, c, …) all fitted to the data. When both dose and square of dose are entered as separate variables in the logistic model, the ratio of their regression coefficients provides a reasonable estimate of α/β according to Thames et al. [31].

Non-linear regression was used with standard linear–quadratic Poisson or probit models (with and without inhomogeneity corrections) to solve for values of ln K (log of the number of clonogens), α, β, and α/β [23,31]. Forms of the linear–quadratic formula used were:

$$P(\text{obliteration}) = \exp[-\exp(\ln K - \alpha D - \beta D^2] \quad (3)$$

$$(\text{obliteration}) = \exp\{ -\exp[\ln K - \beta(\alpha/\beta)D - \beta D^2]\} \quad (4)$$

where $\exp(x) = e^x$, D is the marginal dose, and coefficients to be optimized are: ln K, the log of the number of clonogens; β, the quadratic coefficient for dose; α, the linear

Table 1
Univariate logistic regression analysis of persistent out-of-field AVM nidus after radiosurgery[a]

Variable	*P*(out-of-field nidus)
Prior embolization	0.0181*
Spetzler grade	0.1741
Prior hemorrhage	0.2118
Nidus volume	0.2122
Stereotactic MR and angiography	0.5481
Prior surgery	0.8628

[a] *indicates a significant value ($P < 0.05$).

coefficient for dose (Eq. (3) only), $\alpha\beta$, α/β ratio (Eq. (4) only).

3. Results

We documented overall obliteration by angiography in 193/264 (73%) AVM, and by MR alone in 75/87 (86%) AVM. The corrected obliteration rate was 75%, assuming an eventual 96% true negative rate for MR flow detection [21]. We compared initial stereotactic angiographic and MR images to those at retreatment or follow-up to determine whether the persistent nidus was inside or outside the initial radiosurgery treatment volume. We classified residual nidus as being located out-of-field in 29/83 (35%) of the unobliterated cases and in-field in 54/83 (65%) unobliterated cases.

3.1. Factors associated with of out-of-field nidus persistence

Failure to visualize part of the AVM nidus and include it in the initial radiosurgery target volume resulted in out-of-field nidus persistence in 29/351 (8.3%) patients. Table 1 lists the results of univariate logistic regression analysis.

Table 2
Multivariate logistic regression analysis of post-radiosurgery in-field AVM obliteration as assessed by angiography alone (angiographic: $n = 264$), or both MR and angiographic criteria (MR or angiography: $n = 351$)[a]

Variable	*P*(angiographic)	*P*(MR or angiography)
Marginal dose	0.0093*	0.0029*
Marginal dose squared	0.0190*	0.0072*
Sex (male vs. female)	0.0025*	0.0273*
Patient age	0.7698	0.3530
Cobalt-60 source age (dose-rate)	0.9661	0.6558
Prior hemorrhage	0.2208	0.2170
Prior embolization	0.8350	0.8588
Treatment isodose	0.1582	0.0546
Spetzler AVM grade	0.6988	0.3067
Prior surgery	0.6394	0.1597
Treatment volume	0.4244	0.6967
Stereotactic MR and angiography	0.9468	0.9488

[a] *indicates a significant value ($P < 0.05$).

Out-of-field nidus persistence correlated only with prior embolization in univariate and multivariate analysis ($P = 0.006$, odds ratio = 3.34, 95% confidence interval: 1.46–7.64). We found persistent out-of-field nidus in 18.5% (10/54) of previously embolized patients compared to 6.4% (19/297) of patients with no prior embolization.

3.2. Factors associated with in-field nidus obliteration

We identified in-field nidus obliteration in 220/264 (83.3%) patients with follow-up angiography and 54/351 (83.5%) patients using either angiographic or MR criteria for obliteration. The results of multivariate stepwise logistic regression analysis are shown in Table 2. In the 264 patients with complete angiographic follow-up, multivariate logistic regression correlated with in-field angiographic obliteration with marginal dose ($P = 0.0093$), square of the marginal dose ($P = 0.0190$) and sex ($P = 0.0025$, 106/139 women vs. 114/125 men with obliteration). Similar results were obtained in the multivariate logistic regression analysis of in-field MR or angiographic obliteration, which correlated with marginal dose ($P = 0.0029$), square of marginal dose ($P = 0.0072$), and sex ($P = 0.0273$, 146/186 women vs. 147/165 men obliterated). Fig. 1 shows the logistic dose–response curves for AVM obliteration in men and women. With these dose–response curves, the probability of obliteration reaches a maximum level at marginal doses of approximately 23 Gy.

3.3. Modeling of in-field AVM obliteration

With the above logistic models, the ratios of the regression coefficients for marginal dose and square of marginal dose provide a reasonable estimate of the value of α/β for in-field AVM obliteration [31]. The best-fitting values of $\alpha/$

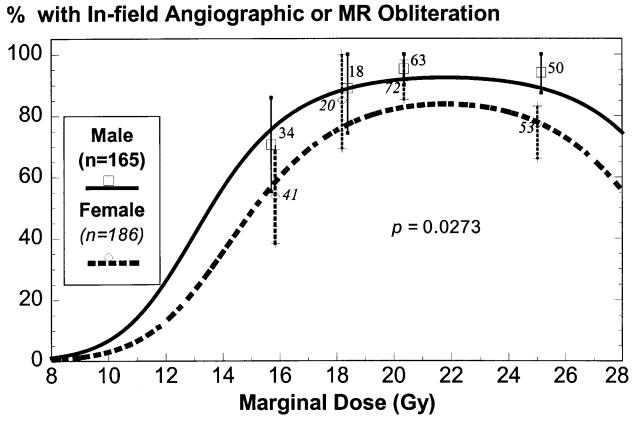

Fig. 1. Logistic dose–response curves for post-radiosurgery, in-field, MR or angiographic AVM obliteration in men ($n = 165$) and women ($n = 186$). The open squares and diamonds represent the percent obliteration at the mean marginal dose for each quartile dose-group of male and female patients, respectively. The number next to each square and diamond represents the number of patients in each dose-group. The numbers for female patients are in italics. The error bars represent the 95% confidence intervals for each quartile dose-groups.

β for angiographic obliteration and for MR plus angiographic obliteration (Fig. 2) for the above empirically derived logistic models (including sex) were $\alpha/\beta = -44.4 \pm 12.5$ and $\alpha/\beta = -45.3 \pm 9.8$, respectively. These values correspond closely to those derived using standard linear–quadratic Poisson models, which were: $\alpha/\beta = -48.1 \pm 5.9$ and $\alpha/\beta = -49.3 \pm 5.3$, respectively. We obtained the same values of α/β from using (α/β, and ln K) as when we used (β, α/β, and ln K) as unconstrained parameters in the standard linear–quadratic Poisson model. When we used an inhomogeneity model with the standard error of α, SE(α) as a free parameter, SE(α) converged to zero, resulting in the same values of α/β, α, β, and ln K for both angiographic obliteration and MR plus angiographic obliteration [23]. From the MR plus angiographic obliteration data, the values of α/β, α, β, and ln K were 0.807 ± 0.299, -0.0164 ± 0.0076, and 7.66 ± 2.85, respectively. Maximum obliteration occurs at 21.75 Gy with the logistic model and 24.75 Gy with the standard linear–quadratic Poisson model.

3.4. Overall obliteration probability: composite in-field dependent model

As stated above (Eq. (1)), the probability of obliterating an AVM with radiosurgery can be obtained by multiplying the marginal dose-dependent probability of in-field obliteration (as calculated from the formulas in Section 2) by the one of the probabilities of not leaving residual out-of-field nidus (according to prior embolization history) as specified subsequently:

$$1 - P(\text{miss, no embolization}) = 0.946 \quad \text{and}$$
$$1 - P(\text{miss, with embolization}) = 0.815 \tag{5}$$

Multiplying these values by the linear–quadratic Poisson in-field AVM obliteration probabilities (Fig. 2) gives the dose–response curves for patients with and without prior embolization shown in Fig. 3.

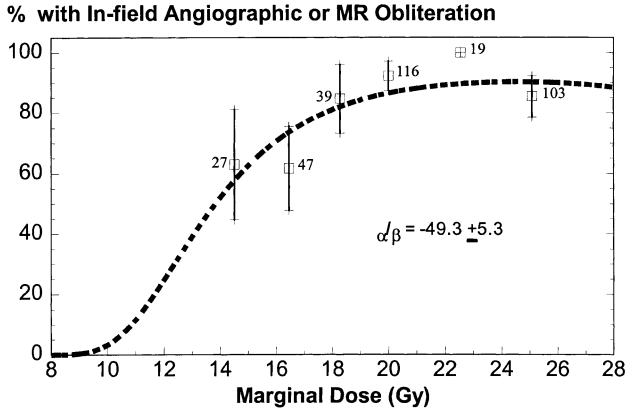

Fig. 2. Standard linear–quadratic Poisson dose–response curve for post-radiosurgery, MR or angiographic AVM obliteration of all patients (male and female, $n = 351$). Each square and associated error bar represents the percent obliteration rate with the respective 95% confidence interval for each of six marginal dose-groups at the mean marginal dose value for each group. The number next to each square represents the number of patients in each dose group.

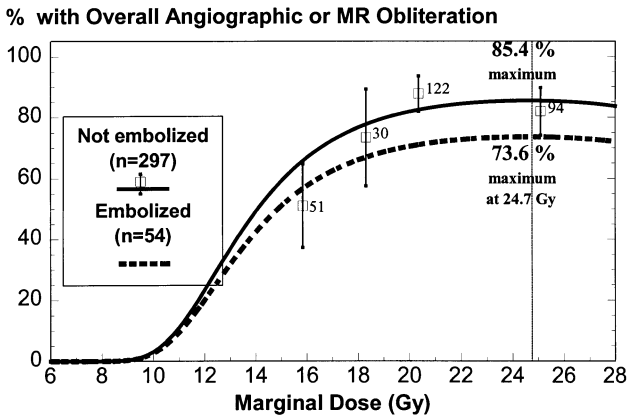

Fig. 3. Comparison of dose–response curves for overall obliteration from the composite in-field obliteration dependent probit linear–quadratic model ($\alpha/\beta = -49.3$) for patients with ($n = 48$) and without ($n = 303$) histories of prior embolization. The squares and error bars represent the percent obliteration rates at the mean marginal dose and 95% confidence interval for non-embolized patients by quartile dose groups. The numbers patients in each dose-group are listed next to the squares.

3.5. Overall obliteration probability: maximum obliteration rate model

Because there is a potential for error in assessing in-field vs. out-of-field nidus persistence, we constructed a model for overall obliteration independent of in-field obliteration determination that incorporates significant factors from the prior analyses (dose, square of dose , history of prior embolization).

3.6. Maximum obliteration rate model

$$P(\text{overall obliteration}) = (\text{MaxOblit} - \text{EmboMiss})\exp\{ - \exp[\ln K - \beta\,(\alpha/\beta)D - \beta D^2]\} \tag{6}$$

where $\exp(x) = e^x$, D the marginal dose, and the coefficients to be optimized are: MaxOblit, the maximum obliteration rate without embolization; EmboMiss, the additional risk of marginal miss from prior embolization (EmboMiss = 0 for patients with no prior embolization); ln K, the log of the number of clonogens; β, the quadratic coefficient for dose; α/β, the alpha/beta ratio.

Sex was left out of the model to limit the number of parameters because of its marginal significance and greater chance of type I error in ascribing statistical significance, and therefore was not included in our initial hypothesis.

Non-linear regression analysis was used to fit parameters to the model. The maximum obliteration rate without embo-

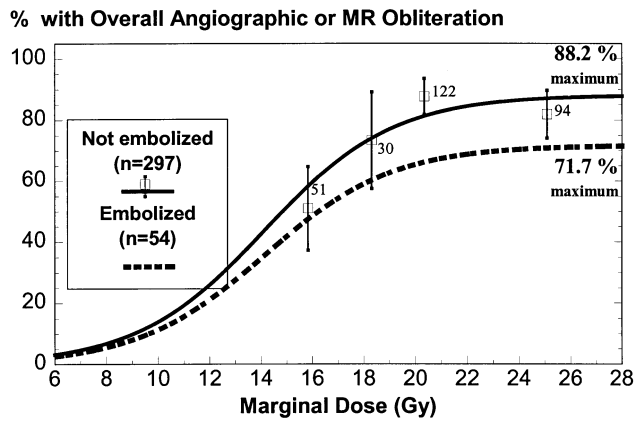

Fig. 4. Comparison of dose–response curves from the maximum obliteration rate model ($\alpha/\beta = 0$) for overall obliteration rates in patients with ($n = 48$) and without ($n = 303$) histories of prior embolization. The squares and error bars represent the percent obliteration rates at the mean marginal dose and 95% confidence interval for non-embolized patients by quartile dose groups. The numbers patients in each dose-group are listed next to the squares.

lization (MaxOblit) was narrowly defined at $87.9 \pm 4.9\%$ ($P < 0.0001$). The additional risk of marginal miss due to embolization (EmboMiss) was $16.4 \pm 7.6\%$ ($P = 0.03$). Prior analysis dependent on in-field obliteration assessment found risks of marginal miss with and without embolization of 18.5 and 5.4% compared to 28.5 and 12.1%, respectively, with the maximum obliteration rate model. The first half of the maximum obliteration rate model defines that 6.7% more unembolized patients ($12.1 - 5.4\%$) will not be obliterated regardless of the dose administered while the composite in-field dependent model adds this limitation to the in-field obliteration curve through the negative α/β coefficient. The β coefficient for square of marginal dose was well defined with the maximum obliteration rate model at $\beta = 0.00964 \pm 0.004114$ ($P = 0.015$). The fit for the number of clonogens was less well defined: $\ln K = 1.58 \pm 0.98$ ($P = 0.11$). The value of α/β was poorly characterized. It converged to zero ($\alpha/\beta = 0 \pm 13$) when constrained to positive values.

The obliteration rate model was relatively insensitive to values of α/β when the values of other parameters were optimized to fit the dose–response. We compared the dose–response curves generated with $\alpha/\beta = 0$ ($\alpha = 0$) to curves fitted to $\alpha/\beta = \infty$ ($\beta = 0$). Between 0 and 40 Gy the median difference in predicted obliteration rates was 0.8% with a maximum of 5.7% at 9 Gy. Between 13 and 25 Gy, the median difference in predicted obliteration rates was 0.5% with a maximum of 1.0% at 15 Gy. Fig. 4 shows the dose–response curve for the maximum obliteration rate model for $\alpha/\beta = 0$ and Table 3 compares the overall obliteration rates predicted at specific doses for the maximum obliteration rate formula those predicted by the composite in-field obliteration dependent formula. Although the predictions of both are similar within the range of marginal doses used in the clinic (15–25 Gy), the maximum obliteration rate model seems preferable because it does not depend on data from an imprecise endpoint (in-field obliteration) and makes better clinical and radiobiological sense (no decrease in obliteration above 25 Gy and no negative value for α/β).

3.7. Multivariate assessment of overall obliteration

We analyzed overall obliteration with stepwise multivariate logistic regression to compare the predictions of the maximum obliteration rate model with the *K*-index and to look for any factors significantly affecting obliteration that were not included in the model. The *K*-index was reported by Karlsson to correlate with AVM obliteration in the Karolinska experience [13,14]. Only marginal dose ($P = 0.0002$) was significant in the first model, which did not include the maximum obliteration rate model predictions. The prediction of obliteration rate from the maximum obliteration rate model was the only factor significantly correlating with overall obliteration, when it was included in the second analysis. We found trends for increasing overall obliteration correlating with increasing age ($P = 0.0546$, odds ratio = 1.19 per decade, 95% confidence interval: 0.998–1.43) and decreasing overall obliteration with prior hemor-

Table 3
Comparison of overall AVM obliteration rate predictions by marginal dose prescribed (Gy) for patients with and without prior embolization predicted by the in-field obliteration dependent (in-field) model with $\alpha/\beta = -49.3$ (predictions in italics) and the maximum obliteration rate (Max Oblit) model with $\alpha/\beta = 0$

Marginal dose (Gy)	Percentage obliterated, embolized patients, in-field model	Percentage obliterated, embolized patients, Max Oblit model	Percentage obliterated, not embolized, in-field model	Percentage obliterated, not embolized, Max Oblit model
12.0	20.1	22.4	23.4	27.6
14.0	42.5	35.8	49.3	44.1
16.0	57.6	48.9	66.9	60.1
18.0	66.0	58.9	76.7	72.5
20.0	70.5	65.3	81.8	80.3
22.0	72.7	68.7	84.4	84.5
23.0	73.2	69.7	85.0	85.7
24.0	73.5	70.3	85.3	86.5
26.0	73.3	71.0	85.1	87.4

rhage ($P = 0.0561$, odds ratio = 0.57, 95% confidence interval: 0.33–1.01). Overall obliteration was less correlated with sex ($P = 0.195$), volume ($P = 0.741$), or *K*-index ($P = 0.864$). Factors already included in the maximum obliteration rate model (marginal dose and history of prior embolization) were not expected to correlate with overall obliteration in the multivariate model incorporating maximum obliteration rate model predictions.

3.8. Subset analysis

In order to discern whether obliteration rates were significantly higher at 20–24 Gy compared to 25 Gy, we performed a subset analysis of patients with AVM treated to these marginal doses. A significantly higher proportion (126/135 or 93.3%) of AVM receiving marginal doses of 20–24 Gy (mean dose 20.7 Gy) achieved in-field obliteration compared to the 85/100 that achieved in-field obliteration after a marginal dose of exactly 25 Gy ($P = 0.034$ chi-square, $P = 0.049$ two-sided Fisher exact). The proportion of patients achieving overall obliteration did not significantly differ between these two groups (113/135 or 83.7% for 20–24 Gy vs. 81/100 at 25 Gy, $P = 0.589$ chi-square).

4. Discussion

Obliterating an AVM by radiosurgery is a complex task that results in a complex radiobiological response. To properly analyze the clinical radiobiology of AVM obliteration, we separated the analysis of the complex task or operation undertaken (correctly identifying all of the AVM nidus and including it within the treatment volume) from the radiobiological dose–response analysis of the irradiated target. By combining the results of these two analyses, we constructed models to predict the radiosurgical obliteration of an arteriovenous malformation based on the marginal dose prescribed and history of prior embolization. Several of the findings in the analyses of out-of-field nidus persistence and of the radiobiological dose–response were unexpected and require further discussion.

4.1. Out-of-field nidus persistence or marginal miss

We found the probability of out-of-field nidus persistence significantly correlated with prior embolization (increased the risk from 6.5 to 18.5%) but did not significantly correlate with any of the other factors examined. We initially hypothesized that embolization would increase the risk of out-of-field nidus persistence because embolization can make delineation of the remaining AVM nidus less clear and because embolized portions of the AVM nidus (normally not included in the target volume) can recanalize. We initially hypothesized that treatment volume might be important factor in marginal misses but there was only a slight correlation ($P = 0.2122$), and that might be explained by our policy of embolizing only large-volume AVMs. We also felt that a history of prior hemorrhage might increase the risk of marginal miss due to temporary compression and/or obliteration of nidus. Prior hemorrhage did not correlate with out-of-field nidus persistence ($P = 0.212$) but there was a trend for decreased overall obliteration with prior hemorrhage in the multivariate analysis ($P = 0.0561$, odds ratio = 0.57, 95% confidence interval: 0.33–1.01). The additional stereotactic 3-D information from adding MR to angiography for stereotactic targeting undoubtedly improves target definition [2,3]. We were surprised to find that it did not significantly decrease out-of-field nidus persistence or decrease overall obliteration. We previously found that adding stereotactic MR to angiography for target definition did not significantly reduce complications [8]. In patients who had only angiography for stereotactic imaging, we consulted prior non-stereotactic MR scans to estimate the 3-D shape of the AVM nidus from the stereotactic angiograms. The use of prior non-stereotactic MR seems to have provided enough information in combination with stereotactic angiography to define the nidus well enough for radiosurgical obliteration and limit complications through reducing normal tissue irradiation that we could not detect any outcome differences. More precise definition of the treatment volume with stereotactic MR imaging allows more precise determination of whether residual nidus was in-field or out-of-field. This could result in small areas of adjacent residual nidus being classified as out-of-field that would have been classified as in-field persistence with only angiography. This effect would obscure any true reduction in marginal misses (out-of-field nidus persistence) with the addition of stereotactic MR. We nevertheless continue to recommend adding high-resolution stereotactic MR to angiography for target definition because we believe it results in more reliable AVM targeting than non-stereotactic, lower resolution images.

4.2. Unexpected results in analyzing in-field obliteration

We did not expect to find a significantly higher rate of radiosurgical in-field AVM obliteration in men than women in this study. It was not validated in the analysis of overall obliteration ($P = 0.195$). This factor needs to be investigated in other series. If sex were to be validated as an independent risk factor for unsuccessful in-field obliteration of AVM after radiosurgery, the most plausible explanation would be that female hormones exert a partial protective effect on the vasculature.

We found the dose–response curve for in-field AVM obliteration fit a linear–quadratic model with an unexpected high negative value ($\alpha/\beta = -49.3 \pm 5.3$) rather than an expected value for CNS tissue of $\alpha/\beta = 1.5$ to 3 from fractionated studies [12,16]. The α/β values derived in this study were highly consistent whether just angiographic or both MR plus angiographic obliteration were used as endpoints. The results were similar using the standard Poisson linear–quadratic formula with or without an inhomo-

geneity correction or whether we used the logistic approximation to the linear–quadratic formula that was empirically derived out of multivariate analysis. If one views the linear–quadratic formula as an empirical approach to curve fitting (part of a power series), it would make sense to have negative β values. Similarly, if one regards this as curve fitting for a single fraction dose–response, one would not expect to extrapolate the results to fractionated treatment or find α/β ratios that match those from fractionated studies. On the other hand, if the linear (α) and quadratic (β) components to the formula represent the double-stranded and single-stranded DNA breakage components, respectively, of the dose–response, then negative β values (and negative α/β ratios) make no sense.

There is a plausible explanation for a dose response that peaks and then starts to drop at higher doses. AVM obliteration requires that a certain level of injury be achieved that causes enough proliferation of intimal and adventitial cells to obliterate the AVM nidus. As higher doses of radiation start killing the cells that we need to proliferate, the obliteration response could potentially drop off with increasing dose. Similar effects occur when high dose intracoronary radiation is used to prevent restenosis after balloon dilatation of coronary arteries [33]. Contrary to the composite in-field obliteration dependent models in this paper, we expect that eventually, higher doses should increase obliteration AVM through the creation of tissue necrosis. We found that maximum doses of 50 Gy (25 Gy to the 50% isodose volume created with 8-mm diameter collimators caused necrosis in some baboons [1].

Another explanation for a plateau in a dose–response curve (which is commonly invoked for tumors) is heterogeneous tissue response. Since AVMs are essentially birth defects composed of individually normal (non-tumor) cells, we expected little tissue heterogeneity compared to that expected in treating tumors. When we added a heterogeneity correction (the standard error of alpha, SEα) for the dominant parameter in the linear–quadratic in-field obliteration model as a free parameter, the value converged to zero, leaving α/β unchanged. It could be argued that a more extensive heterogeneity model should be used incorporating SE(β) and SE(K). We felt the model already contained too many parameters when a heterogeneity correction for the dominant parameter, α, was added. On the other hand, the maximum obliteration rate model we constructed could serve to model a small fraction of radioresistant AVM (up to 7% of unembolized AVM patients) that would not obliterate with in the dose range studied of 12–26 Gy.

A final possible explanation for the negative β value, which reflects the lower in-field obliteration rates at 25 Gy than 20–24 Gy, is that there may be differences in the imaging characteristics between these groups, such as less distinct nidus definition in the higher dose group. Our dose-prescription policy restricted 25 Gy marginal doses for AVM with the smallest volumes. Therefore, there certainly was a volume difference (mean volume: 2.87 cm^3 for 20–24 Gy vs. 1.62 cm^3 for 25 Gy). When angiography alone was used for initial stereotactic imaging, there may have been a greater tendency to assign cases of persistent nidus just outside the radiosurgery treatment volume as in-field persistence for smaller volume (higher dose) AVM.

4.3. The maximum obliteration rate model

The maximum obliteration rate model seems to provide a reasonable mathematical description of overall AVM obliteration that removes the uncomfortable requirement for a negative value of α/β to properly fit the dose–response observed. The initial component describing a maximum obliteration rate, regardless of dose administered, describes the plateau (below 100%) seen in the dose–response curve. It seemed to be explained primarily by the potential for error in targeting the AVM nidus. If this was the only problem then the obliteration rate could be theoretically raised to 100% by the use of large treatment margins and high doses, but this would lead to unacceptable complications. As indicated by the multivariate analysis of overall obliteration, the initial component of the formula describing maximum obliteration may need to include other factors such as history of prior hemorrhage ($P = 0.055$) if future analyses can show them to have a significant effect.

It was disappointing that the value of α/β for AVM obliteration was not narrowly defined with the maximum obliteration rate model. The complexity of the response and the number of factors affecting it that needed to be modeled were the main reasons for this difficulty. If $\alpha/\beta = 2$, then the contribution from the α component would only be approximately 10% of the total dose-effect for the bulk of the data around the median dose of 20 Gy. If α/β is closer to zero, the α component contribution becomes miniscule making α (and α/β) even more difficult to define. Despite our difficulty defining α/β, the dose–response curve predicted by the maximum obliteration rate model seems reliable since it is relatively insensitive to the value of α/β when other parameters in the model are optimized. The value of α/β could not be reliably determined in this study and the best-fitting value of $\alpha/\beta = 0$ chosen for the dose–response curves in Fig. 4 should not be used to calculate equivalent doses for fractionated irradiation of AVM. It is doubtful if the linear–quadratic formula with any value for α/β obtained from a single-fraction dose–response analysis would be reliable enough to extrapolate from high-dose single fraction irradiation to fractionated radiotherapy.

4.4. Summary

The rate of AVM obliteration from radiosurgery depends on the marginal dose administered with a dose–response curve that reaches a maximum of approximately 88%. The dose–response plateau may be explained at least in part by difficulty with target definition and depends on factors such as history of prior embolization. Because of the limited improvement in the rate of obliteration predicted for doses

above 23 Gy and the general principle that complications increase with increasing dose, we recommend that doses higher than 25 Gy not be used. Observations that need further study include the lower in-field obliteration rates that we observed in women (which did not translate into significantly different overall obliteration rates than men), the effect of prior hemorrhage and age on overall obliteration rates, and the exact value of α/β for AVM obliteration.

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