Decision analysis for small, asymptomatic intracranial arteriovenous malformations

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Object. Asymptomatic intracranial arteriovenous malformations (AVMs) represent a clinically challenging problem because of the complex decision making that must be undertaken prior to beginning any type of treatment. In addition, the relative infrequency of these lesions means that there is relatively little experience reported in the literature. The authors use a decision-analysis technique to model the considerations that go into determining the treatment of these lesions in an effort to quantify the various risks and overall benefits conferred by the following three treatment strategies: observation/natural history, microsurgery, and stereotactic radiosurgery.

Methods. The authors conducted a thorough literature search to elucidate the risks and outcomes associated with each treatment option. These values were used to build and run a comprehensive Markov model to determine a base-case analysis. All of the input variables were also subjected to sensitivity analysis to identify the most influential input variables and the crossover points in which favored strategies changed.

The base-case analysis suggested that microsurgery was the favored treatment option because this hypothetical cohort accumulated 21.53 quality-adjusted life years (QALYs) over the course of the model compared with the 16.97 QALYs and 16.40 QALYs for stereotactic radiosurgery and observation, respectively. Sensitivity analysis demonstrated that overall major neurological morbidity and mortality were the most influential input variables both perioperatively and during the radiosurgical "latent" period (that is, up to 2 years posttreatment). The maximum acceptable perioperative combined major neurological morbidity and mortality rate was 6.8%. The latent period combined major neurological morbidity and mortality would need to be 0.7% to make radiosurgery favorable in this analysis.

Conclusions. Results of this decision analysis model suggest that microsurgery in the hands of experienced cerebrovascular surgeons, who can expect a less than 6.8% combined rate of major neurological morbidity and mortality, offers patients a greater overall quality of life over time.

KEY WORDS • arteriovenous malformation • natural history • decision analysis •
Markov model • neurosurgery • radiosurgery

Asymptomatic intracranial AVMs are heterogeneous lesions that vary in size and location and possess different arterial supplies and venous drainage patterns. They are congenital lesions and therefore represent an entire lifetime of risk to a patient, a risk believed to be relatively constant. The specific risk, is hemorrhage, which can lead to outcomes of death, major neurological deficits, minor neurological deficits, or no problem at all. These possible outcomes appear to occur in predictable rates of patients when hemorrhages occur. Long-term, well-controlled studies in which therapeutic interventions are studied are difficult to design or conduct because these lesions are relatively uncommon and clinical experience with their treatment is limited.

Intervention for AVMs is, at the core, a statistical proposition. The decision is made to intervene because the

likelihood of long-term benefit is outweighed by the short-term risks of the procedure. The decision is difficult because various therapeutic interventions are available for patients harboring such lesions, each with its own risk-benefit profile. In this type of difficult decision-making situation, the tool of decision analysis has frequently been used to aid in making appropriate choices.^{3,7} In this decision analysis the idea is to break down the larger decision into its possible outcomes and to assign a mathematical probability to them. The probabilities can be assigned using the known experiences as reported in the literature. Based on this information, a model can be constructed in which the total value of each individual pathway to an overall outcome will be known. Finally, the most favorable pathway can be chosen for a given clinical situation and the accuracy of this choice challenged through sensitivity analysis in which each input factor is varied through its range of possible values.^{1,8,9,23,24,26,27,31,37}

Decision analysis has been used to approach AVM treatments in the past for exactly these reasons.^{10-12,19,20}

Abbreviations used in this paper: AVM = arteriovenous malformation; QALY = quality-adjusted life year; QOL = quality of life.

Historically, the decision analyses that have been completed have been flawed because the complexity of the decision was not considered or because information concerning the risks and benefits of various treatment options was absent. Ultimately, these analyses become outdated as new information becomes available concerning the risks and benefits of each treatment approach. Iansek, et al.,²⁰ published one of the earliest decision analyses on the treatment of AVMs in which the results suggested that observation was favored over excision. In this study the surgery-related mortality was estimated at 10% and major neurological morbidity at 27%.²⁰ The accuracy of these numbers could not be challenged by comparison with data from the literature at the time. Moreover, an accurate range could not be established for the purposes of sensitivity testing. In a subsequent decision analysis performed by Fisher¹¹ the author found lower surgery-related morbidity (8.99%) and mortality (5.54%) estimates and, thus, that surgery was the favored strategy over observation. At the times of his studies, the author did not have the benefit of the more detailed information about natural history and the stratification of the surgical treatment-related risk that has been provided by the Spetzler–Martin grading system. Further studies have since been conducted which confirm surgery as the favored strategy, often with the option of radiosurgery embedded in the analysis.^{13,28,34}

What follows is an attempt to review and update the process of decision analysis for AVMs. Consideration is given to the most recent material available concerning the natural history of these lesions and the risks and benefits associated with their different treatment modalities. The analysis is limited to Spetzler–Martin Grade I to III AVMs because no consensus for treating larger lesions has emerged.

CLINICAL MATERIAL AND METHODS

Decision Analysis and the Markov Model

To analyze the treatment decision appropriately, we must construct a comprehensive model that deals with all possible outcomes and implications of each possible treatment decision over the course of a hypothetical cohort of patients' lives.^{8,9,24,26,27,37}

We used a computer-supported Markov model (Tree-Age Software Inc., Williamstown, MA) to examine the clinical outcomes of hypothetical patients with AVMs managed by one of three strategies: observation, radiosurgery, or microsurgery. Such a clinical treatment option analysis can be presented in the form of a simple decision tree. Each decision node allows the clinician to evaluate the accepted prognosis for the patient if given Treatment 1 compared with Treatment 2 or 3. The patient's predicted outcome or resulting health status translates into the "utility" of each option. As hypothetical patients are run through the model, they move between a set of mutually exclusive health states during each cycle, which represents 1 year of life. Each health state, one of which is death, is associated with an "incremental utility" that enumerates the relative value of being in that state compared with another. A transition from one state to another is associated with the "transition probabilities" of clinical events each year and is dependent on the choice of treat-

ment, health state of the patient in the previous year, and the patient's age. The total incremental utility generated by the cohort for a given year is found by multiplying the utility value for each state by the fraction of the cohort within that state and then summing across all of the states. For our purposes, this value is in units of QALYs. If a monetary value is used in addition, the model becomes a cost–benefit analysis as well. This becomes particularly important when the decision path that provides the greatest number of QALYs is also more costly. The cumulative utility is defined as the running sum of the total incremental utility generated during each year. As the years from the decision increase, more of the patients will make the transition to death, both because of the adverse effects of treatment and because of the accepted natural life expectancy of the cohort. Thus, fewer individuals will contribute to the cumulative utility. Ultimately, the model will terminate because all patients will die. The conclusions of the base case can be subjected to sensitivity analysis. By testing a range of values for each entered variable, sensitivity testing identifies the factors most influential on the model as well as the crossover points where different strategies become more favorable.

Assumptions and Definitions

The first step is to define outcomes and make underlying assumptions. For the purposes of this analysis, asymptomatic is defined as having no AVM-related symptoms at the time of evaluation. It is the unusual patient presenting for evaluation in whom an AVM is a completely incidental finding. Nevertheless, because the reasons for presentation are not taken into consideration here, patients who may have exhibited symptoms in the past that led to their presentation can still be considered in the analysis provided they were asymptomatic at the time of analysis. This way, all patients are entered into the model with an equal QOL.

Cure is defined as angiographically demonstrated obliteration of the lesion, whether this is accomplished by surgery or stereotactic radiosurgery, and is considered to provide complete protection against future hemorrhage. Any hemorrhage is considered to cause at least a minor neurological deficit. Because all patients are equally exposed to the risk posed by diagnostic angiography, this risk is not factored into the model. Natural life expectancy is factored into the model because all patients will eventually die even if they experience no untoward AVM-related events. The patients entered into the analysis must start from a specific age so that they have equivalent life expectancies. For the purposes of this model, we used the age of 35 years because this is the mean age of patients in all the natural history studies used.

The probabilities of each individual outcome and health state were established by analyzing the literature associated with each intervention. For the purposes of this study, the therapeutic modalities considered were those with adequate data available for comparison, specifically microsurgery, stereotactic radiosurgery, and observation (equivalent to the natural history of the disease). Because embolization has not been shown to be an effective treatment on its own, it was not used as a separate arm in the model.^{30,40}

The possible health states used in the model are death, major neurological deficit, minor neurological deficit, and wellness. These were defined prior to developing the model based on a review of the literature on the natural history of the lesion, and the definitions were used to screen the subsequent studies from which data served as “inputs” to the therapeutic arms of the model. The numerical value for each health state’s utility was assigned based on the literature review as well. The definition of death is self-evident and its value of 0 is intuitive. Major neurological deficit is defined as any deficit that permanently decreases the patient’s ability to lead his or her previous life (a value of 0.39). A minor neurological deficit is defined as any transient deficit or a permanent deficit that does not interfere with a patient leading his or her normal life, and well is defined as the absence of a neurological deficit or event (a value of 0.95 for both). The parity in these values was chosen to indicate that living with a lesion represents a less than perfect QOL, but there is no difference in value because in either case the patient is leading his or her normal life. Minor neurological deficits are treated in the model with a disutility (a subtraction) of three months instead of an overall reduction in QOL. The methodology behind establishing these variables has been published elsewhere.³⁵

Review of the literature was also used to determine the transition probabilities for each outcome as well as the probabilities of the specific risks and benefits for each treatment strategy. In cases of observation, the benefit is no risk of an intervention. Examples of these risks include a perioperative morbidity or mortality as well as a radiation-induced neurological injury that occurred in radiosurgical intervention. There is no protection from the risk of the lesion bleeding, however, and thus it is the downside to such strategy.

In cases of surgery, there is a risk associated with performing the procedure. A certain small percentage of patients are expected to suffer from a perioperative neurological deficit, either major or minor, and some will die of procedure-related causes. The cure attainable with a complete resection justifies the perioperative risk and is the benefit of this treatment option.

Stereotactic radiosurgery is a more complicated option to address. In all cases of radiosurgery, there is thought to be a lower perioperative risk because it does not involve a craniotomy. The benefit of stereotactic radiosurgery is a time-dependent obliteration of the AVM, which provides complete protection from risk in a percentage of patients. The mechanism behind its effectiveness involves the gradual proliferation of the endothelium in the abnormal vessels receiving the radiation dose. Until the proliferation results in complete obliteration of the lesion, however, the risk remains at the level of the lesion’s natural history, with the possibility of hemorrhage and the possibilities of a neurological deficit (major or minor) or death in cases in which hemorrhages do occur. This raises the issue of the time required for complete obliteration of the lesion as well as the overall percentage of patients cured at the end of this period of time, both of which were established and incorporated into the model.

Sensitivity Analysis

To test the accuracy of these results, the model was sub-

jected to sensitivity analysis. The concept behind this is to vary the individual inputs to the model within an acceptable range, shown in Table 1. If the preferred strategy does not change while varying an input, then that input is relatively unimportant to the overall decision-making process. Conversely, if the preferred strategy does change, then the value of the input at which the strategy becomes less favorable can be identified. Such a crossover point can represent the goal that a treatment must attain to become preferred or the morbidity at which a preferred treatment is no longer acceptable.

RESULTS

Natural History

The available literature was reviewed extensively to identify studies in which the natural history of AVMs was assessed. In the majority of reports the authors characterized the outcomes as well, minor neurological deficit, major neurological deficit, and dead (Table 2). Slight adjustments to the numerical data were made to enable comparison between and among studies and to make all denominators equivalent. Occasionally, there were more levels of neurological deficits, and in such studies interpretation was required to classify the outcomes into the established categories for the model. Another area in which an adjustment was needed occurred in the category of minor neurological deficit. According to the rules of the model, any hemorrhage resulted in at least a minor neurological deficit. In some studies a hemorrhage that resulted in no deficit was not counted among the minor deficits. These numbers were adjusted upward accordingly, with the higher numbers listed parenthetically in the table. Finally, the total incidence of minor neurological deficits was readjusted down so that the entire incidence of deficits and death was equal to the total number of hemorrhages. This final change was made to ensure that the model ran more smoothly, and sensitivity analysis confirmed that it made no difference in the final output of the model.

Surgical Treatment

Review of the literature readily showed that the Spetzler–Martin grade appropriately characterized the surgery-related risk of an AVM. Although this grading system was developed as a prognostic tool for surgery-related outcome only, most of the studies on surgical treatment and many of the radiosurgical treatment classified the treated AVMs this way. Because the studies listed in Table 3 all

TABLE 1
Summary of ranges determined in the sensitivity analysis

Input Factor	Minimum	Maximum
natural history hemorrhage rate (%/yr)	2.09	11.62
periop morbidity & mortality (%)	0.00	1.12
Spetzler–Martin Grades I–III (%)		
radiosurgical cure rate (%)	5.20	77.36
radiosurgical stroke rate (%/yr)	1.53	6.25
age (yrs)	0	72

TABLE 2
Summary of studies in which the natural history of AVMs was assessed

Authors & Year	No. of Patients	Patient Yrs	No. of Hemorrhages	Death	No. of Cases	
					Major Morbidity	Minor Morbidity*
Forster, et al., 1972	35	420	10	6	4	3
Graf, et al., 1983	191	542	63	17	31	84
Fults & Kelly, 1984	131	722	60	20	8	24 (32)
Crawford, et al., 1986	217	2257	77	31	6	17 (40)
Brown, et al., 1988	168	1378	31	9	18	40
Itoyama, et al., 1989	50	670	14	5	4	5
Ondra, et al., 1990	160	3792	147	37	62	(48)
total	1089	9781	402	125	133	(252)
percent per year			4.11	1.28	1.36	2.58 (1.47)

* Parenthetical values represent the authors' interpretation of each study's reported number of morbidities, reflecting the definitions established for the decision analysis.

used the predefined clinical outcomes (well, minor neurological deficit, major neurological deficit, dead), their data easily conformed to our overall model. Some slight interpretation was required for some studies to make their outcomes analogous and comparable; however, it is clear from Table 3 that there was relatively little variation among the studies examined. The numbers obtained represented a one-time risk of surgery and differed from the life-time risk of hemorrhage and its resultant outcomes used for the natural history arm of the model.

Stereotactic Radiosurgery

This modality is relatively newer than surgery in the treatment of AVMs, and as a result, much of the available literature concerns understanding the treatment parameters in addition to providing overall outcomes.

Data were derived from studies primarily conducted on small AVMs (Table 4). The data summarized in Table 5 refer to the morbidity and mortality seen during the period between the initial treatment and ultimate angiographically demonstrated obliteration, referred to here as the latent period. That these radiosurgery-related rates are better than the those seen in the natural history of AVMs probably represents both a percentage of the lesions in which eventual obliteration occurred and thus a zero risk, during this latent period of observation. Because this was documented in a large number of patients and patient years, it was these risk values that were used in the model.

TABLE 3
Summary of morbidity and mortality rates in surgical series of Spetzler–Martin Grade I to III

Authors & Year	No. of Patients	No. of Cases		
		Death	Major Morbidity	Minor Morbidity
Spetzler & Martin, 1986	69	0	1	4
Heros, et al., 1990	91	1	0	10
Sisti, et al., 1993	67	0	8	24
Hamilton & Spetzler, 1994	76	1	1	8
Pikus & Harbaugh, 1998	54	0	0	1
total (%)	357	2 (0.56)	10 (2.80)	47 (13.2)

Adjustments to these data were made to allow for the fact that many patients did undergo follow-up angiography. The true percentage of angiographically demonstrated AVM obliteration probably lies somewhere between a high of 77.4% and a low of 5.2% shown in Table 5. Nevertheless, 77.4% was used for the model to favor radiosurgery because of its noninvasive nature. The problem was also addressed using sensitivity analysis.

Decision Analysis Tree

After this extensive review of the literature, the formerly roughly approximated model could be constructed with the confidence of specific percentages that could be applied to encompass all possible outcomes. A simplified version of the model is shown in Fig. 1. For each cycle, regardless of the intervention, if the patients were well or suffered only a minor neurological deficit, they were only exposed to life expectancy risks in that cycle. If a major neurological deficit resulted, the life expectancy was lowered and the QOL was adjusted down. Cases in which the patients died could contribute no QALY to the total.

Hypothetical patients undergoing observation were exposed to the risk of life expectancy as well as the risk of AVM-related hemorrhage at the rates reported in the literature for each cycle (year) of the model. In cases in which hemorrhage occurred, the patients progressed into the outcome states of death, major neurological deficit, and minor neurological deficit at the reported probabilities. The appropriate decreases in QOL were applied, and QALYs were totaled for the cycle and the discount rate applied. At the end of each yearly cycle, the hypothetical patients would be reexposed to these risks for the next cycle. The model continued in this fashion, accumulating QALYs until there were no patients left in the cohort.

For hypothetical patients undergoing surgery, the possible outcomes were death, major neurological deficit, minor neurological deficit, or well. Patients were exposed to a one-time risk of the microsurgical procedure after which the model assumed no further risk of AMV-induced hemorrhage.

For the group in which radiosurgery was performed, a latent period of 2 years was imposed. During this time the hypothetical patients would be exposed to life expectancy

TABLE 4
Summary of morbidity and mortality rates in radiosurgical series

Authors & Year	No. of Patients	Patient Yrs	No. of Hemorrhages	No. of Cases		
				Death	Major Morbidity	Minor Morbidity
Betti, et al., 1989	66	80	5	4	2	0
Colombo, et al., 1989	97	138	4	0	1	2 (3)*
Lunsford, et al., 1991	227	265	10	2	10	7
Friedman & Bova, 1992	80	125	2	0	2	6
Steiner, et al., 1992	228	590	9	6	12	16
Pollock, et al., 1994	65	190	5	2	1	3
Karlsson, et al., 1996	1604	2340	49	14	10	25
total	2367	3728	84	28	38	60
percent per yr			2.25	0.75	1.02	1.61

* See Table 3 for definition of parenthetical value.

risks as well as a risk of AMV-induced hemorrhage that was slightly lower than that associated with natural history. This corresponded to the lower risk of hemorrhage reported in the literature for this period of time and almost certainly mirrors the fact that some AVMs become obliterated more quickly than others. At the end of 2 years, 77.4% of the group were considered to be cured and were exposed to only life expectancy risk for the remainder of the model. The other 22.6% were exposed to the natural history risk in addition to life expectancy for the remainder of the model. The QALYs were similarly totaled.

Base-Case Preferred Strategies

For the Spetzler–Martin Grade I to III AVMs the surgical treatment group gained 21.53 QALYs over the course of the model. This compared with the 16.97 QALYs and 16.40 QALYs gained by the stereotactic radiosurgery and observation groups, respectively.

Sensitivity analysis revealed that the only input factors that could change the overall outcome were morbidity and mortality that occurred during the perioperative period and during the latent period in patients who underwent radiosurgery (Fig. 2).

DISCUSSION

Our base-case scenario suggests that microsurgery is

the preferred strategy for the treatment of small intracranial AVMs. A closer examination of the results of the sensitivity analysis shows why. Perioperative morbidity and mortality are the only factors that result in a significant decrease in the number of QALYs accumulated in the surgery cohort. The occurrence of minor neurological deficits causes a small decrease in QOL but does not affect the rate at which QALYs are acquired by this cohort. In the case of morbidity and mortality that occur during the radiosurgical latent period, Figure 3 provides the best demonstration of the effect. This figure illustrates the statuses of patients in the various hypothetical cohorts after the 1st year in the model. At this point, the surgery arm has already been exposed to all of the lesion-related risks that the patients will encounter. Patients in the radiosurgery group, in the meantime, remain completely within the latent period and are considered to be untreated and exposed to risk. At this point, the radiosurgery group is already behind the surgery group in terms of the overall number of acquired QALYs. From this point on, both groups continue to be exposed to the risks of life expectancy; however, the surgery group is exposed to no further AVM-related risk whereas the radiosurgical group remains exposed. Under these circumstances it is clear that the radiosurgery group will never be able to acquire the same number of QALYs as the surgery group. If the rate of hemorrhage could be lowered in this group to 0.7% per year the strategy would cross over to being favorable. Unfortunately, Figure 2 demonstrates that this represents a greater than 50% reduction in the lowest hemorrhage rate reported in the literature. For the patients undergoing radiosurgical treatment to attain this lower rate of hemorrhage, unacceptably high radiation doses are required, which would likely, in fact, induce neurological deficits. A corollary here is that the overall cure rate for radiosurgery has no effect on the final decision because the surgery group is ahead before this even occurs.

The sensitivity analysis also demonstrates the bias of the study. Figure 2 shows the distribution of major and minor morbidity rates (upper limit, lower limit, study rate, and crossover rate). The study rate used for microsurgery is the highest morbidity and mortality rate reported in the literature, whereas that for radiosurgery-related morbidity and mortality is close to the lowest rate reported. This effectively biases the study toward radiosurgery.

TABLE 5
Radiosurgical AVM obliteration rate at 2 years*

Authors & Year	No. of Patients		Complete AVM Obliteration		
			No. of Patients	Percentage	
	Total	Angio		of Angio	of Total
Betti, et al., 1989	66	40	27	68	41
Colombo, et al., 1989	97	20	15	75	16
Lunsford, et al., 1991	227	46	37	80	16
Friedman & Bova, 1992	80	21	17	81	21
Steiner, et al., 1992	228	NS	NS	81	NS
Pollock, et al., 1994	65	32	27	84	42
Karlsson, et al., 1996	1604	NS	NS	NS	NS
total	2367	159	123	77.4	5.2

* Angio = patients who underwent angiography; NS = not stated.

Fig. 1. Simplified decision tree for Spetzler–Martin Grade I to III AVMs.

It has been observed anecdotally that smaller AVMs become obliterated more quickly, than larger lesions because of their size and because they can be given a higher dose of radiation. Analysis of our data on the incidence of hem-

orrhage in the latent interval supports this observation. The rate appears to be lower, and it is easy to postulate that this is related to the fact that a percentage of the lesions have already been obliterated. Unfortunately, there were no sufficient published data on the size of AVMs treated radiosurgically to analyze this variable with sensitivity testing.

Other factors that could be assessed with sensitivity analysis include the natural history stroke rate, the age of the patients entering the study, the values assigned to various outcome states, and the discount rate. The first two factors might change the analysis in terms of the decision between surgery and observation, but they would be unlikely to affect the choice between surgery and radiosurgery. Quality values and discount rates largely function to decrease the difference between two strategies over a long period of time and, as such, would be unlikely to alter the result, which in the case of small AVMs is actually determined after a single cycle (year) of the model.

Other considerations not included in our analysis are the medical comorbidities and the role of radiosurgery for lesions located in eloquent locations. In cases such as these a radiosurgical approach might still be favored. Unfortunately, these aspects are not reported on extensively in the literature and are therefore difficult to treat with decision analysis.

Fig. 2. Sensitivity analysis for mortality and major neurological morbidity. Values listed on the vertical axis represent percentages of the cohort.

Fig. 3. Simplified decision tree for Spetzler-Martin Grade I to III AVMs after one cycle (year).

CONCLUSIONS

We have reviewed decision analysis as a method and presented aspects of a new decision analysis. We have attempted to illustrate the usefulness of this objective approach when considering the treatment options for a given patient with an asymptomatic AVM. We have used the most current data on the natural history of AVMs, and we have used the Spetzler-Martin grading system for the first time in such a study in an attempt to depict more accurately the clinical scenario.

In the future it will be important to make the entire process more accessible to the individual surgeon. Ideally, surgeons, both microsurgical and radiosurgical, should be able to enter into the model the morbidity and mortality rates of the procedures they have performed rather than relying on a standard set by the leaders in the field, whose complication rates might be expected to be lower given their experience. Furthermore, a grading system designed to predict the morbidity of the individual lesion rather than the morbidity associated with a specific treatment of that lesion would be more useful for making appropriate clinical decisions in individualized circumstances. Finally, the ultimate application of this tool would be to enter an individual patient's data. With this type of automation, a decision analysis in which the appropriate risks are addressed could be tailored to an actual clinical situation. Although it is not a substitute for the surgeon's overall clinical judgment or the patient's wishes, such an unbiased, mathematically rigorous, and informative approach would certainly aid in counseling patients harboring dangerous lesions such as AVMs.

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