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Natural History of Cerebral Arteriovenous Malformations and the Risk of Hemorrhage after Radiosurgery

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Abstract

The annual hemorrhage rate of intracranial arteriovenous malformations (AVMs) varies from 2 to 4%. In a patient with decades of life ahead, the cumulative risk of hemorrhage is significant. AVMs exhibiting characteristics such as deep venous drainage, venous stenosis, associated aneurysms and feeders from perforators are associated with an elevated risk of hemorrhage. We reviewed 1,400 AVM patients who underwent Gamma Knife surgery (GKS) at the University of Virginia between 1989 and 2009. The dose selection was based on the size and location of the nidus. The mean prescription dose was 21.2 Gy (range 5–36 Gy), and the mean maximum dose was 39.4 Gy (range 10–60 Gy). A total of 657 patients suffered 803 hemorrhagic events over 42,495 risk years before GKS. Assuming that these patients were at risk for hemorrhage since birth, the annual hemorrhage rate was 2.0%. If we calculate the hemorrhage rate after the diagnosis of the AVMs, the hemorrhage rate was 6.6%. Following GKS and prior to a radiographic documented obliteration, the annual hemorrhage rate was 2.5%; this rate is very similar to the 2.0% one computed prior to radiosurgery by assuming AVMs to be congenital. Once angiographic obliteration was confirmed after GKS, the hemorrhage rate dropped to zero.

In extrapolating from their experience with cerebral aneurysms, early neurological surgeons had been convinced that cerebral arteriovenous malformations (AVMs) had a propensity to rupture and lead to catastrophic sequelae [1]. As such, neurosurgeons were inclined to offer treatment for many patients with accessible AVMs. Prior to the advent of radiosurgery, microsurgically inaccessible lesions had been managed conservatively. In the ensuing decades, some natural history studies on AVMs became available [2–5]. Over time, neurosurgeons came to realize that some but not all AVMs are prone to rupture, and the prognosis was not usually as dismal as with cerebral aneurysms [5].

Later, several studies revealed that AVMs at different locations or with certain angioarchitectural characteristics behave differently. Thus, all AVMs are not the same

and those with a greater risk of rupturing should be treated. Treatment of unruptured but rupture-prone AVMs became more appealing with the emergence of embolization and radiosurgery; these treatment approaches offered a reasonable chance for obliteration and a relatively low rate of procedural complications.

Since the first AVM treated with the Gamma Knife was published in 1972 [6], over 60,000 AVMs have been treated worldwide with radiosurgery. The AVM is not obliterated immediately following radiosurgery. As such, patients are followed closely over the ensuing years. Several large series including some from the University of Virginia have provided a clearer sense of the benefits and risks of stereotactic radiosurgery for AVM patients [7–9]. Pretreatment information from AVM patients provides useful insight into the preradiosurgical hemorrhage risk and the natural history of AVMs. Also, careful follow-up of AVM patients after radiosurgery has led to a thorough understanding of the hemorrhage rate during the latency period before and after obliteration of the nidus.

The first part of this report will focus on the available literature with regard to the natural history of AVMs and the risk factors associated with hemorrhage. The second portion of this report will focus on the hemorrhage rate following radiosurgery.

The Natural History of Arteriovenous Malformations

Even though the prognosis for AVM patients is no longer considered dismal, it is generally accepted that the lifetime risk of hemorrhage remains high, and most AVMs require treatment [10]. As most patients are treated with microsurgery, embolization or radiosurgery, few purely observational studies of AVM patients exist.

In the current literature, 4 major studies were published on the natural hemorrhagic history of untreated AVMs (table 1). In 1986, Crawford et al. [11] published a retrospective study of 217 patients treated conservatively (13 patients did have surgery or embolization at a later point), and, in this study, patients were followed for a mean of 10.4 years. The authors reported a 2% hemorrhage rate. Itoyama et al. [12] reported on 50 patients unsuitable for surgery and noted a similar hemorrhage rate after a mean observation period of 13.4 years. Ondra et al. [4] published their landmark study on 160 patients managed conservatively for an average of 24 years. They reported an annual hemorrhage rate of 4%, and a mortality rate of 1% [4]. Yamane et al. [13] studied 115 patients (including 53 patients with partially treated AVMs) and reported a 4.2% annual hemorrhage rate. Based on these 4 studies, the natural hemorrhage rate of AVMs is widely held to be between 2 and 4%.

In addition to the aforementioned studies, information regarding the hemorrhage risk of AVMs was also provided in series that included a mixture of treated and untreated AVM patients [3, 14, 15]. However, the hemorrhage rates reported by these studies should be viewed more cautiously. Retrospective studies face the difficulty of determining when the patients started to be at risk for hemorrhage. Although AVMs

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Table 1. Hemorrhage rates in untreated cerebral AVMs

Authors	Year	Patients n	Follow-up years	Annual hemorrhage rate %	Accumulated mortality rate %	Risk factors associated with hemorrhage (before/after diagnosis)			
						age	size	location	pregnancy
Crawford et al. [11]	1986	217	10.4	2	29	n.a./old	small/n.a.	deep/n.a.	yes
Itoyama et al. [12]	1989	50	13.4	2.1	10	–	small/n.a.	deep/deep	n.a.
Ondra et al. [4]	1990	160	23.7	4	23	–	–	–	–
Yamane et al. [13]	1998	115	6.5	4.2	10	–	small/large	deep/n.a.	–

n.a. = Not associated; – = not stated.

are considered congenital anomalies and theoretically patients are at risk for hemorrhage since their birth, hemorrhage usually occurs in adolescence or young adulthood. It is believed that AVMs are dynamic lesions with ongoing morphological and hemodynamic changes. Unknown factors may play a significant role in causing rupture later in the progression of the vascular malformations. The hemorrhage rates obtained from these studies tend to be lower due to the assumed longer at-risk period [2, 15].

An alternative approach taken by some is to base the calculation of the hemorrhage rate from the time of diagnosis of the AVM until the date of intervention. Such studies frequently consist of a mixture of patients with large and deep AVMs that were left untreated as well as small, superficial AVMs that were successfully treated. Therefore, most of the follow-up data on hemorrhage risks were contributed by patients with large and deep AVMs. Such a selection bias may limit the value of the hemorrhage risk calculations. Also, AVMs tend to exhibit a higher rebleeding rate at least for some period of time following a previous hemorrhage. Including patients during a period of heightened risk for hemorrhage (i.e. hemorrhagic clustering) may overestimate the hemorrhage rates and not be reflective of the 'natural history' of AVMs in several papers [16, 17]. Despite these limitations, such studies do provide valuable insight into AVM behavior; these studies reveal a hemorrhage rate that ranges from 2.4 to 13% (table 2).

Predicting Risk Factors of Arteriovenous Malformation Hemorrhage

As previously noted, not all AVMs have a similar risk of hemorrhage. A number of retrospective studies have compared patients with or without hemorrhage as the presentation symptom. These studies have identified clinical features that affect hemorrhage

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Table 2. Hemorrhage rates in series with treated and untreated cerebral AVMs and risk factors of hemorrhage

Authors	Year	Patients n	Follow-up years	Annual hemorrhage rate %	Risk factors associated with hemorrhage after diagnosis	
					related	not related
Graf et al. [3]	1983	191 (120/71)	2/4.8	6/2–3	old age small AVMs[1]	size
Brown et al. [2]	1988	168 (0/168)	8.2	2.2		size
Mast et al. [18]	1997	281 (142/139)	0.7/1.0	13/2	deep vein prior hemorrhage	age size
Stefani et al. [19]	2002	390 (146/244)	3.1	3.2	large AVMs deep location deep draining vein single draining vein deep feeders	prior hemorrhage
Halim et al. [20]	2004	790 (367/423)	2.3/5.4	3.7/1.4	prior hemorrhage	size deep draining vein
Stapf et al. [21]	2006	622 (282/340)	2.3	2.8	old age deep location deep draining vein prior hemorrhage	size aneurysm
Yamada et al. [22]	2007	305 (159/146)	2.4/3.5	6.8/3.1	young age deep location prior hemorrhage	size deep draining vein
Hernesniemi et al. [23]	2008	238 (139/99)	13.5	2.4	large AVMs deep location	draining vein
Da Costa et al. [24]	2009	678 (258/420)	2.9	7.5/4.2	deep draining vein aneurysm prior hemorrhage	age size deep location deep draining vein

For patient number, follow-up and annual hemorrhage rate, when appropriate, data are presented as hemorrhagic cases/nonhemorrhagic cases.

[1] Size was not related to hemorrhage in patients who presented initially with hemorrhage, but small size was a predicting factor in patients with nonhemorrhagic presentation.

risk: young age, smaller size and deep location may increase the risk of hemorrhage [25–28]. Certain angioarchitectural characteristics such as deep venous drainage, venous stenosis, associated aneurysms and feeders from perforators have also been reported to be associated with an increased risk of nidus rupture. The hemorrhage risk related to nidus size has been the subject of debate [26–28]. However, most studies have failed to demonstrate a significant relationship between hemorrhage risk and

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the AVM volume. It is probable that smaller volume AVMs are less likely to cause focal neurological deficits or headache, and thus are diagnosed only after a more dramatic event such a seizure or a hemorrhage. Other factors such as deep location and its associated features (deep feeders and deep draining veins), unsecured aneurysms, and prior history of hemorrhage are consistently associated with an increased risk of hemorrhage.

Hemorrhage Risk before and after Radiosurgery

Whether radiosurgery reduces the risk of AVM rupture during the latency period remains controversial. Various studies report that AVM hemorrhage risks are [15, 29–31] decreased [16, 30], unchanged [15, 32] or increased [29, 31, 33] after radiosurgery. The incidence of postradiosurgical hemorrhages has been reported to be between 1.7 and 4.8% [15–17, 30, 32, 34, 35]. Since there is no control group in such studies, the best way to compare the postradiosurgical hemorrhage rates would be using the numbers from published natural history studies (e.g. 2–4% annual risk). Using a hemorrhage rate of 2–4%, there does not seem to be significant change of hemorrhage rate following radiosurgery until the AVM is obliterated.

It is widely accepted that radiosurgical obliteration confers a substantial benefit in terms of preventing future hemorrhages. However, the benefit of radiosurgery in terms of reducing hemorrhage in the latency period (i.e. prior to obliteration) remains the subject of much debate. Since it is difficult if not impossible to conduct a randomized control study, it is tempting to compare the postradiosurgical hemorrhage rates to the preradiosurgical rates. Maruyama et al. [16] reported a 54% decreased risk of hemorrhage following radiosurgery. However, as previously mentioned, the major concern is that the preradiosurgical hemorrhage risk could represent an overestimation. It is not clear whether the decrease in hemorrhage rate is just the natural decline of risk after an initial hemorrhage or truly a beneficial effect of radiosurgery.

For example, we can use a simple method to recalculate the hemorrhagic rates in the paper of Maruyama et al. During the preradiosurgical period, there were 42 hemorrhages in 500 patients within a median follow-up of 0.4 years (the mean was not provided and since the authors mentioned most patients were treated soon after hemorrhage, we assumed that the median is close to the mean); the annual hemorrhage is almost 20% (42 events in 200 risk-years) This hemorrhagic rate is extremely high. The authors observed 23 hemorrhages in 458 patients within a median of 2 years after radiosurgery and reported a postradiosurgical hemorrhage rate of 2.5%. The authors utilized alternative statistical methods to define a ‘significant’ reduction of the hemorrhage rate after radiosurgery. Although they note that the recurrent hemorrhage rate is stable over 3 years following an initial hemorrhagic episode, the patient and event numbers are too small to draw a definite conclusion.

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Table 3. Hemorrhage rates in radiosurgery series and risk factors of AVM hemorrhage

Authors	Year	Patients n	Annual hemorrhage rate (birth to radiosurgery) %	Annual hemorrhage rate after radiosurgery %	Risk factors for hemorrhage after radiosurgery	
					related	not related
Pollock et al. [15]	1996	315 (196/119)	2.4	4.8 (within 2 years)	unsecured aneurysm	location size draining vein prior hemorrhage dose
Friedman et al. [32]	1996	199 (121/78)		4.4	unsecured aneurysm large AVMs venous stenosis periventricular location low dose	age prior hemorrhage
Karlsson et al. [36]	2001	1,593		1.8 (within 2 years)	old age large AVMs low dose	location aneurysm prior hemorrhage
Nataf et al. [35]	2004	756 (423/333)	1.8	3.1	unsecured aneurysm large AVMs prior hemorrhage complete coverage low dose	
Maruyama et al. [16]	2005	500 (318/182)	2.0	2.5		
Liscak et al. [37]	2007	330 (207/123)	2.5	2.1		
Kaliswal et al. [34]	2008	160 (103/57)	2.5	1.7		

For patient number, when appropriate, data are presented as hemorrhagic cases/nonhemorrhagic cases.

Most studies examining the natural history of AVMs actually have demonstrated a temporary period of increased risk of hemorrhages once an AVM ruptures [18, 20, 22, 24] In a subsequent study, Maruyama et al. [17] calculated the hemorrhage rate considering AVMs as congenital lesions, and they reported a preradiosurgical hemorrhage rate of 2%. There is no doubt that the 2.5% hemorrhage rate they reported following radiosurgery is similar to their 2% preradiosurgical rate and the natural history. Therefore, whether radiosurgery provides protective effects from AVM rupture before AVM obliteration remains uncertain given the evidence currently available (table 3).

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Hemorrhage from Arteriovenous Malformations Confirmed Obliterated on Angiography after Radiosurgery

Magnetic resonance imaging (MRI) is currently the most widely used imaging modality to assess the AVM response after radiosurgery and provides a high positive predictive rate of nidus obliteration [15]. Angiography is still recommended by most neurosurgeons to confirm complete obliteration of the nidus before a patient can be declared 'cured'. Total obliteration of the AVMs after radiosurgery was defined by Lindquist and Steiner [38] as 'complete absence of pathological vessels in the former nidus, disappearance or normalization of afferent and efferent pathological vessels, and a normal circulation time on high-quality rapid serial subtracted angiography'. It is generally accepted that once the nidus is obliterated based on a high-quality angiography, the risk of hemorrhage is essentially eliminated.

Lindquist et al. [39] reviewed 48 patients in whom follow-up cerebral angiography was performed 4–17 years after the AVM had previously been deemed obliterated. They reported 4 patients who had experienced hemorrhage despite documentation of AVM obliteration [39]. The hemorrhage was from a recanalized nidus in 2 patients, a new AVM appearing adjacent to the previously treated nidus in 1 patient and unknown in 1 patient. Maruyama et al. [16, 17] reported 4 patients with hemorrhages 16–51 months after angiographic confirmation of AVM obliteration. Two patients underwent surgery. Histopathology revealed small residual AVM vessels in addition to the occluded AVM. The blood vessels showed typical radiation-related thickening of the intima and dense hyalinization of the vascular lumen. The authors reported that continuous contrast enhancement of the treated nidus on computed tomography (CT) or MRI is a risk factor for hemorrhage despite angiographic obliteration of a nidus. Others have been unable to confirm this finding, and instead note that persistence of contrast enhancement at the target site of radiosurgery may persist for many years after angiographic confirmation of obliteration.

Recurrent AVMs following a complete surgical resection have also been reported [40]. Similar to the cases reported in radiosurgical series, this phenomenon is more common in pediatric AVM patients. The significance of this rare event in pediatric patients with AVMs warrants further investigation, but may be related to the persistence of blood vessel growth factors in the growing child.

The Experience with Arteriovenous Malformations at the University of Virginia

Patient Population

A total of 1,400 AVM patients who underwent Gamma Knife surgery (GKS) at the University of Virginia between 1989 and 2009 have been reviewed. The large patient number and relatively long-term follow-up allowed us to investigate the

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postradiosurgical hemorrhage rate and retrospectively the hemorrhage rate of AVMs before GKS. Our follow-up protocol was magnetic resonance images every 6 months for 2 years then yearly thereafter. When MRI showed that there was no flow void visible, cerebral angiography was recommended to confirm obliteration of the nidus. CT or MRI was performed if patients developed new or worsened symptoms such as headaches, seizures or neurological deficits. Hemorrhagic events in this study were defined as clinically symptomatic events with signs of hemorrhage on either CT or MRI. Additionally, asymptomatic hemorrhages which were only identified on follow-up images were also included. The clinical information was obtained from examining the patients or from patients' referring physicians or families.

Because the purpose of the present report is also to investigate the effect of GKS on the hemorrhage rate, 105 patients with large AVMs which were only partially treated were excluded from analysis. Additionally, 91 patients lost to follow-up were excluded leaving 1,204 AVM patients in the present study for analysis.

Patient Demographics and AVM Characteristics

There were 637 males and 567 females with a mean age of 35.3 years (range 3–82 years). The initial presentations leading to the diagnosis of AVMs were hemorrhage in 605 (50.2%), seizures in 271 (22.5%), headache in 163 (13.5%), neurological deficits in 89 (7.4%) and other symptoms (e.g. vertigo, bruits, tinnitus) in 33 (2.7%). In 43 (3.6%) patients, the AVMs were incidental findings. Additionally, 50 patients who initially presented with symptoms other than a hemorrhage experienced at least 1 episode of bleeding between the diagnosis of their AVMs and GKS. One hundred and thirty-eight patients had a partial resection of the nidus and 298 underwent a partial embolization of the nidus before undergoing GKS.

The locations of the AVMs were in the cerebral hemispheres in 742 (61.6%), basal ganglia in 92 (7.6%), thalamus in 104 (8.6%), corpus callosum in 47 (3.9%), brainstem in 99 (8.2%), cerebellum in 90 (7.5%) and insula/sylvian fissure in 30 (2.5%) patients. The Spetzler-Martin grading of the AVMs were grade I in 204 (16.9%) patients, grade II in 455 (37.8%) patients, grade III in 452 (37.5%) patients, grade IV in 91 (7.6%) patients and grade V in 2 (0.2%) patients. The nidus volume ranged from 0.1 to 33 cm^3 (mean 3.4 cm^3). The venous drainage was superficial only in 600 AVMs, deep only in 475 and both deep and superficial in 129. Five hundred and thirty-five AVMs had multiple draining veins, and 669 had only a single dominant draining vein.

Gamma Knife Radiosurgery Technique

The Gamma Knife model U was used from 1989 until July 2001 when the C model replaced it. The Perfexion model was used after September 2009. The Kula system was used for treatment planning from 1989 to 1994 and then was replaced with Gamma Plan software. Stereotactic angiography was the only imaging modality available in

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the beginning for dose planning, and, in the early 1990s, MRI was added for target definition and dose planning.

The dose selection is based on the size and location of the nidus. The mean prescription dose was 21.2 Gy (range 5–36 Gy), and the mean maximum dose was 39.4 Gy (range 10–60 Gy). The mean isodose configuration was 55% (range 30–95%), and the mean number of isocenters was 2.8 (range 1–22).

Statistical Analysis

The annual hemorrhage rate was calculated as the number of hemorrhages divided by the patient-years at risk. The pre-radiosurgical hemorrhage rates were calculated in two ways. First, we assumed that patients were at risk for hemorrhage since their birth and the risk years were calculated from their birth dates to the dates of GKS. The pre-radiosurgical hemorrhage rates were calculated as total hemorrhagic events divided by the sum of patients' ages at the time of GKS. Alternatively, we calculated the risk of hemorrhage starting from the dates that the AVMs were diagnosed until the dates of GKS.

We have not observed any patients having a hemorrhage after the nidus had been declared obliterated based on angiography; therefore the rate of postradiosurgical annual hemorrhage was calculated by dividing the hemorrhagic events by the patient risk years for which the end points were the dates of nidus obliteration or the dates of last follow-up if the nidi remained patent. As the nidus should have become obliterated before the final image study concluding obliteration of the nidus, we assumed that the AVMs became obliterated at the midpoint between the dates of the last images showing the AVMs were still patent and the dates of the first images showing that the AVMs were obliterated. We chose the dates when the AVMs were concluded obliterated on MRI instead of angiograms because some patients refused to have follow-up angiography to confirm the nidus obliteration and angiography was usually performed after the MRI had suggested that the nidi had become obliterated. If errors were to be introduced by incorrectly judging that the nidus had become obliterated based on MRI, we actually avoided overestimating the patient-years at risk and therefore underestimating the hemorrhage rate.

Univariate and multivariate logistic regressions were used to test for an association with patient demographics (age, gender) and AVM characteristics (size, lobar vs. deep locations, superficial only vs. deep venous drainage, single vs. multiple draining veins) with hemorrhagic AVM presentation. Univariate and multivariate proportional hazard models were used to test the risk factors predisposing patients to hemorrhage in the period from the diagnosis of AVM to the date of GKS and the follow-up period after GKS. Patients were censored from the postradiosurgery bleeding risk group when the AVM was obliterated. In addition, they were censored if patients underwent repeat GKS, surgical resection or embolization after GKS, were lost to follow-up or died. Additional factors evaluated for hemorrhages from diagnosis to GKS included hemorrhagic or nonhemorrhagic presentation. Radiosurgical

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treatment parameters (i.e. prescription dose, maximum dose, isodose configuration, number of isocenters) were further added to evaluate the postradiosurgical risk of hemorrhage.

Outcome of GKS

The mean imaging follow-up was 71 months following GKS. GKS yielded a total angiographic obliteration in 584 (48.5%) and subtotal obliteration [41] (residual draining vein without visible nidus on angiography) in 43 (3.6%) patients. In 429 (35.6%) patients, the AVMs remained patent. In 148 patients (12.3%) no flow void was observed on MRI, but patients either had not reached the time point when the angiography should be performed or they refused to have follow-up angiography to confirm the obliteration of the nidus. If we exclude 151 patients with follow-up less than the 2 years of latency period, angiographic obliteration occurred in 55.5%, subtotal obliteration in 4.1%, no flow void on MRI in 14.1%, and the nidi remained patent in 26.4%.

Preradiosurgical Hemorrhage Rate and Rebleeding Rate

A total of 657 patients suffered 803 hemorrhagic events over 42,495 risk years before GKS assuming patients were at risk for hemorrhage since their birth. Five hundred and fifty-six patients had one, 74 had two, 20 had three, and 7 had four or more episodes of hemorrhages. The crude annual hemorrhage rate was 2.0%. If we calculate the hemorrhage rate after the diagnosis of the AVMs, there were 68 hemorrhages in 52 patients who initially presented with symptoms other than hemorrhage and 130 rebleeds in 90 patients who experienced hemorrhages leading to the diagnosis of AVMs. The hemorrhage rate calculated after the diagnosis of the AVMs is 6.6% (198 bleeds in 2,984 risk years).

We also calculated separately the hemorrhage rate in patients who initially presented with hemorrhage or other symptoms before diagnosis of the AVMs. The hemorrhage rate in the subgroup of 605 patients who initially presented with hemorrhage was 735 events divided by 19,712 risk years yielding a 3.7% annual hemorrhage rate assuming patients were at risk for hemorrhage since their birth. The hemorrhage rate would be 10.4% if we calculated the 130 hemorrhagic events in 1,243 risk years from the diagnosis of AVMs to the dates of GKS. In the subgroup of 599 patients who initially presented with symptoms other than hemorrhage, 52 patients experienced 68 episodes of hemorrhages between the diagnosis of AVMs and the time of GKS. The hemorrhage rate was 3.9% (68 events divided by 1,741 risk years) from the diagnosis of AVMs to the date of GKS (fig. 1).

In patients with prior hemorrhages, the annual rebleeding rate was 8.6% (146 hemorrhages in 1,581 risk years from the dates of initial hemorrhage to the dates of GKS). The rebleeding rate was 10.2% in the first year after the initial hemorrhage, 10.8% in the second year, 6.5% between the second and fifth years, 6.7% between the fifth and tenth years, and 8.8% after 10 years. The rebleeding rate was approximately

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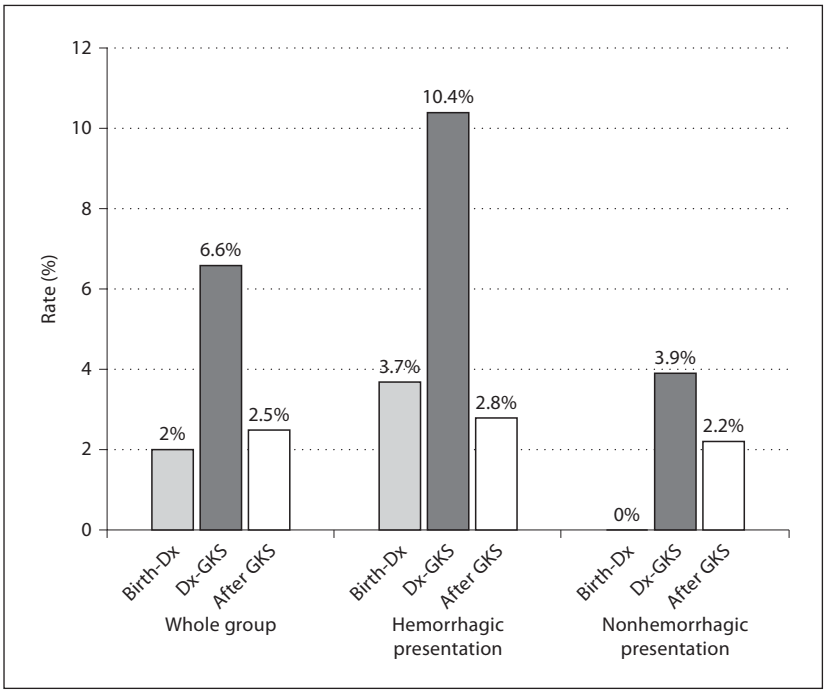

Fig. 1. Hemorrhage rates before and after GKS in patients who experienced at least 1 hemorrhage before GKS. Dx = Diagnosis.

10% in the first and second years; it decreased but remained elevated in the first 5 years after an initial hemorrhage.

Patient Demographics and AVM Characteristics in Hemorrhagic or Nonhemorrhagic Presentation

Patients tending to present with hemorrhage were those of younger age, smaller volume AVMs in deep locations, and those with deep venous drainage or only a single draining vein (table 4). The same risk factors were checked for the period between the diagnosis of the AVMs and GKS. After the initial diagnosis, small and deep AVMs were no longer associated with an increased risk of hemorrhage, thereby suggesting that small and deep AVMs were more likely to be diagnosed after a hemorrhage, but that the small size or deep location were truly independent risk factors predisposing AVMs to rupture (table 5). A single draining vein was a risk factor for hemorrhage prior to and after the initial diagnosis. Patients with a prior hemorrhage are more likely to have a subsequent hemorrhage. Of 605 patients who had a hemorrhage leading to the diagnosis of the AVM, 90 developed a subsequent hemorrhage before GKS. Of the 599 patients who did not present with hemorrhage at the time of the diagnosis of the AVMs, 50 subsequently developed a hemorrhage ($p < 0.001$).

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Table 4. Patient demographics and AVM characteristics in patients with hemorrhagic or non-hemorrhagic presentation

	Nonhemorrhagic presentation (n = 599)	Hemorrhagic presentation (n = 605)	p value (univariate)	p value (multivariate)
Patient demographics				
Male/female	316/283	321/284	0.916	
Age, years	35.2±15.7	30.6±16.7	<0.001	<0.001
AVM characteristics				
Location				
Lobar/deep	481/118	351/254	<0.001	<0.001
Venous drainage				
Superficial only/deep venous drainage	376/223	224/381	<0.001	<0.001
Single/multiple draining veins	278/321	391/214	<0.001	<0.001
Volume of the nidus, cm^3	4.0±3.3	2.8±3.0	<0.001	<0.001

Table 5. Risk factors of hemorrhages between the diagnosis of AVM and time of GKS

	No hemorrhage after diagnosis (n=1064)	Hemorrhage after diagnosis (n=140)	p value (univariate)	p value (multivariate)
Patient characteristics				
Male/female	564/498	73/69	0.693	–
Age of hemorrhage, years	33.5±16.2	28.5±15.9	0.858	–
AVM characteristics				
Location				
Lobar/deep	754/308	78/64	<0.001*	0.119
Venous drainage				
Superficial only/deep venous drainage	545/517	55/87	0.006*	0.774
Single/multiple draining veins	579/483	90/52	<0.001*	0.016*
Volume of the nidus, cm^3	3.4±3.3	3.6±2.8	0.060	–
Prior hemorrhage (no/yes)	547/515	52/90	<0.001*	<0.001*

Asterisks indicate statistically significant p values.

Postradiosurgical Hemorrhage Rate and Risk Factors of Hemorrhage

Following GKS, 94 patients had a hemorrhage, and 18 patients had 2. The postradiosurgical hemorrhage rate is 2.5% (130 hemorrhagic events in 5,239 risk years). The hemorrhage rate was 2.3% within 2 years following GKS, 2.2% between the second and fifth years, 2.5% between the fifth and tenth years, and 4.0% between the tenth and twentieth years (fig. 2). The postradiosurgical hemorrhage rate is fairly comparable to the reported natural hemorrhage rate of 2–4%.

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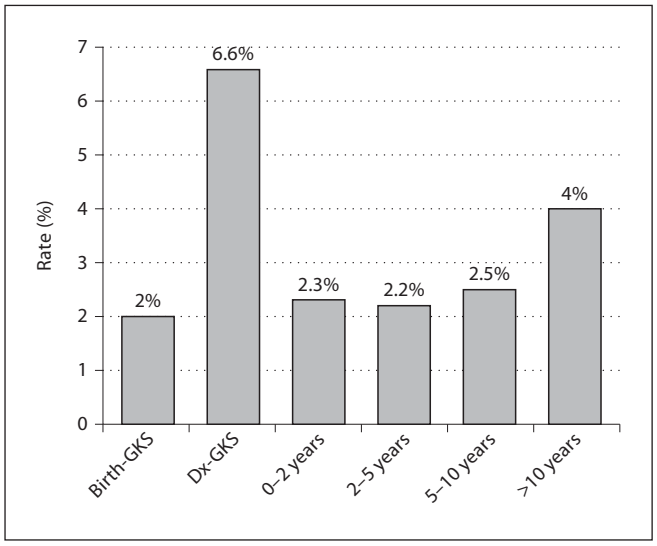

Fig. 2. Annual hemorrhage rates before and after GKS in our institutional experience for those with nonobliterated AVMs. Dx = Diagnosis.

In the subgroup of patients with preradiosurgical hemorrhage, 55 patients had 1 and 12 patients had 2 hemorrhages following GKS. The postradiosurgical hemorrhage rate in this subgroup was 2.8% (79 hemorrhagic events in 2,868 risk years) which seems to be lower than the preradiosurgical hemorrhage rates (3.7% calculated since birth or 10.4% calculated after diagnosis of the AVMs; fig. 1). The reduction of the hemorrhage rate from 10.4 to 2.8% seems to be quite significant. However, as we mentioned earlier, these data should be interpreted with caution since most believe that there is a temporarily increased risk for a subsequent hemorrhagic risk in the immediate period following a prior hemorrhage. Therefore, the reduction of the hemorrhage rate following GKS might represent the natural history of sporadic and temporal clustering of hemorrhages from AVMs.

Risk Factors Predicting Hemorrhage after GKS

Risk factors for at least 1 postradiosurgical hemorrhage were deep location, large nidus size and low prescription dose in univariate analysis. In multivariate analysis, only a low prescription dose remained to be associated with a high risk of hemorrhage (table 3). Of 657 patients who had a hemorrhage before GKS, 67 (10.2%) had hemorrhage during the follow-up. Of the 547 patients who did not have hemorrhage before GKS, 45 (8.2%) developed a hemorrhage during the follow-up ($p = 0.142$). Our institutional experience seems to be in keeping with the study from Karlsson et al. [42] showing that a low radiation dose is related to a continued risk for post-treatment hemorrhage. Higher doses of radiation trigger radiobiological pathways that lead to endothelial and perhaps intimal proliferation, decreased vessel diameter,

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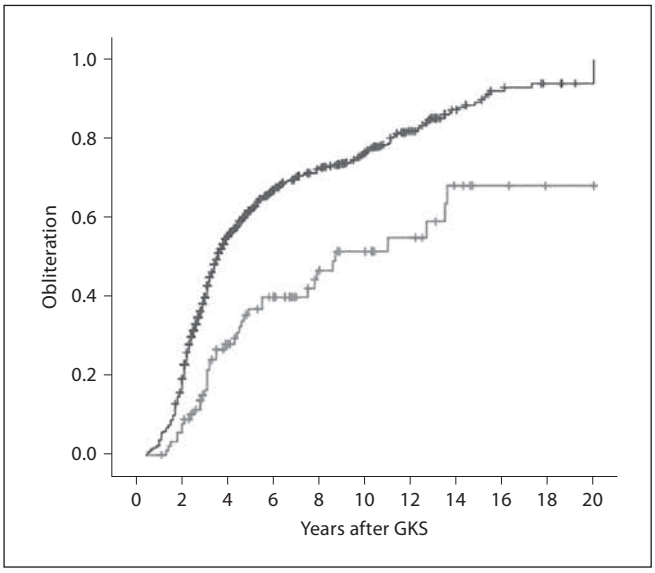

Fig. 3. Kaplan-Meier curves showing a higher obliteration rate in patients who did not have postradiosurgical hemorrhages (upper curve) compared to those with postradiosurgical hemorrhages (lower curve).

Table 6. Risk factors for a hemorrhage following Gamma Knife surgery

	No hemorrhage after GKS (n=1092)	Hemorrhage after GKS (n=112)	p value (univariate)	p value (multivariate)
Patient characteristics				
Male/female	581/511	56/56	0.928	–
Age of hemorrhage, years	35.4±16.1	34.4±17.0	0.826	–
AVM characteristics				
Location				
Lobar/deep	766/326	66/46	0.015*	0.271
Venous drainage				
Superficial only/deep venous drainage	546/546	54/58	0.982	–
Single/multiple draining veins	614/478	55/57	0.787	–
Prior hemorrhage (no/yes)	502/590	45/67	0.156	
Initial treatment parameters				
Volume of the nidus, cm^3	3.3±3.1	4.7±4.0	0.035*	0.214
Prescription dose, Gy	21.4±3.3	19.5±3.7	0.006*	0.046*
Maximum dose, Gy	39.6±7.3	37.4±6.9	0.231	–
Isodose line, %	55.2±11.4	52.6±8.4	0.081	–
Isocenters, n	2.8±2.2	2.9±1.7	0.480	–

Asterisks indicate statistically significant p values.

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and eventual AVM obliteration [43]. A low dose of radiation delivered to an AVM is generally an ineffective dose as a peripheral dose of less than 16 Gy seldom achieves AVM obliteration.

Hemorrhage and AVM Obliteration

Among 1,054 patients with a follow-up of at least 2 years, the AVM obliteration rate (based on MRI or angiography) is lower in patients with postradiosurgical hemorrhage (fig. 3). In 92 patients with postradiosurgical hemorrhage, 51 (55.4%) AVMs remained patent at the last follow-up (mean follow-up 106.8 months, range 24–240 months). In 962 patients without hemorrhage, 271 (28.2%) AVMs remained patent ($p < 0.001$). None of our patients had sustained a hemorrhage following angiographic confirmation of AVM obliteration.

Conclusions

The natural hemorrhage rate in AVMs ranges from 2 to 4%, and the rate seems to be somewhat elevated in the immediate period following a prior hemorrhage. Although small AVMs are more likely to present with hemorrhage, smaller AVMs do not seem to be associated with a high hemorrhage rate once the AVMs have been diagnosed. Deeply located AVMs are more consistently associated with a hemorrhagic presentation as well as a higher rate of hemorrhage following their diagnosis. Other angioarchitectural features such as deep draining veins, venous stenosis or unsecured aneurysms are also associated with a higher hemorrhage rate.

Our experience and a review of the literature provide further evidence that patients remain at risk for hemorrhage as long as the nidus remains patent after radiosurgery. Although we have not observed a recurrent hemorrhage as long as the nidus was found to be obliterated based upon angiography, sporadic case reports of postobliteration hemorrhage call for continuous follow-up of the AVM patients even after radiographic confirmation of nidus obliteration.

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