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Hemorrhage from Arteriovenous Malformation Following Gamma Knife Radiosurgery: Pathophysiology of Rupture Early in the Latency Period

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1. Introduction

Arteriovenous malformations (AVM) are uncommon congenital abnormalities with a prevalence of 10-18 per 100, 000 adults (Al-Shahi et al. 2002; Berman et al. 2000) and an incidence of 1. 3 per 100, 000 person-years. (Stapf et al. 2003) Arteriovenous malformations typically present with hemorrhage, seizure, or focal neurological deficit. Intracranial hemorrhage is the most common clinical presentation of an AVM, resulting in significant morbidity and mortality. The natural risk of primary hemorrhage in untreated AVMs is 2% to 4% per year. (Barrow and Reisner 1993; Brown et al. 1988; Crawford et al. 1986; Davis and Symon 1985; Forster, Steiner, and Hakanson 1972; Fults and Kelly 1984; Graf, Perret, and Torner 1983; Mast et al. 1997; Ondra et al. 1990; Pollock et al. 1996) The primary goal of AVM treatment is elimination of the risk of hemorrhage by removal of the bleeding potential of the abnormal vasculature. Currently, the therapeutic options for AVM treatment include microsurgical resection, stereotactic radiosurgery (SRS), and endovascular embolization, alone or in combination. Small AVMs or those that are surgically inaccessible in deep brain or eloquent cortex are typically amenable to stereotactic radiosurgery.

Complete obliteration of the vascular malformation and concomitant elimination of the risk of hemorrhage are the goals of radiosurgical treatment for AVM. There is generally a latency period of 2 to 3 years to achieve the vessel obliteration that results from radiation-induced changes to the abnormal vasculature, and 80%-95% of patients will achieve angiographic obliteration by 5 years. (Colombo et al. 1994; Friedman, Bova, and Mendenhall 1995; Karlsson, Lindquist, and Steiner 1997; Lindqvist et al. 2000) During the interval from treatment to AVM obliteration, a risk of rupture persists, but there is debate as to the direction and magnitude of the influence of radiosurgery on the risk of AVM hemorrhage during the latency period. Conflicting reports in the literature provide evidence for a decreased risk of hemorrhage, (Karlsson, Lax, and Soderman 2001; Karlsson, Lindquist, and Steiner 1996; Kjellberg et al. 1983; Levy et al. 1989; Maruyama et al. 2005; Maruyama et al. 2007; Yen et al. 2007) an unchanged risk of hemorrhage, (Friedman et al. 1996; Kjellberg 1986; Lunsford et al. 1991; Maesawa et al. 2000; Nataf et al.

2004; Pollock et al. 1996; Steiner et al. 1992) and an increased risk of hemorrhage. (Colombo et al. 1994; Fabrikant et al. 1992; Steinberg et al. 1990) There is also evidence that a risk of hemorrhage persists even after radiographic obliteration of the AVM. (Izawa et al. 2005; Lindqvist et al. 2000; Matsumoto et al. 2006; Shin et al. 2005; Yamamoto et al. 1992; Prat et al. 2009)

Hemorrhage in the early period following SRS is a rare occurrence, with few reports in the literature (Table 1). In the 30-day period following SRS, most reported cases of post-radiosurgery hemorrhage within 72 hours of radiosurgery occurred in patients with irradiated tumors. (Franco-Vidal et al. 2007; Izawa et al. 2006; Park et al. 2000; Suzuki et al. 2003; Uchino et al. 2003) There is only one report of AVM hemorrhage within 72 hours following SRS. (Nataf et al. 2004) Within 4 to 30 days following SRS there are a few more documented cases of post-radiosurgery AVM hemorrhage. (Chang et al. 2004; Colombo et al. 1994; Pollock et al. 1994; Shimizu et al. 2001; Shin et al. 2004; Yen et al. 2007; Zabel-du Bois et al. 2007; Celix et al. 2009) With two exceptions, the cases reported in the literature of AVM hemorrhage in the early period following radiosurgery are presented in the context of retrospective observational cohort studies and the clinical and radiographical details of the cases are not described. One published case report of rupture of a pial AVM 29 days following SRS was associated with pretreatment partial thrombosis of a distal draining vein varix. (Shimizu et al. 2001) The authors of this chapter recently published a case of AVM hemorrhage occurring 9 days after gamma knife radiosurgery, with radiographic documentation of venous thrombus formation immediately preceding intracranial hemorrhage. (Celix et al. 2009) We posit that the pathophysiology of AVM rupture in the early period following SRS differs from rupture occurring months after radiosurgery.

There is a substantial literature on AVM hemorrhage and the associated factors that increase hemorrhage risk both prior to treatment and following radiosurgery. Clinical and morphological risk factors for AVM rupture during the latency period have been proposed, but little is known about the mechanism of and risk factors for hemorrhage in the early period following radiosurgery. The histological effects of radiation on abnormal AVM vessels, the resultant alterations in cerebral hemodynamics, and the timing of vascular changes in relation to the timing of AVM rupture post-radiosurgery have not been extensively studied, but the available literature evidence supports the association among tissue irradiation, acute inflammatory response, and vessel thrombosis in the pathophysiology of early hemorrhage following AVM radiosurgery.

2. Risk factors for AVM hemorrhage – Untreated AVMs

Based on observational studies, there are several characteristics that are hypothesized to predispose to hemorrhage in untreated AVMs. Patient age (Crawford et al. 1986; Graf, Perret, and Torner 1983; Karlsson et al. 1997; Mast et al. 1997) and pregnancy status (Dias and Sekhar 1990; Forster, Kunkler, and Hartland 1993; Horton et al. 1990; Robinson, Hall, and Sedzimir 1974) are proposed factors with insufficient evidence to support their association with an increased risk of AVM hemorrhage. Arteriovenous malformation size (Crawford et al. 1986; Graf, Perret, and Torner 1983; Guidetti and Delitala 1980; Itoyama et al. 1989; Kader et al. 1994; Karlsson et al. 1997; Langer et al. 1998; Parkinson and Bachers 1980; Spetzler et al. 1992; Waltimo 1973) and AVM location (Crawford et al. 1986; Duong et al.

Author	Dx	Treatment Modality	Study Type	Prescription Dose (Gy) Range, Mean	Maximum Dose (Gy) Range, Mean	Isodose Line (%) Range, Mean	Age (yrs), Sex	Time Course	Outcome
Celix 2009	AVM	GK	CR	18	36	50	57, M	9 Day	Died
Zabel-du Bois 2007	AVM	LINAC	Cohort	15 - 22, 18 (Median)	(18.8 - 27.5)†	80	NR, NR	6 Day	NR
Yen 2007	AVM	GK	Cohort	15 - 31, 22.5	22 - 90, 41.3	30 - 91, 50 (Median)	NR, NR	30 Day	NR
Franco-Vidal 2007	VS	GK	CR	13	(26)†	50	20, M	24 Hr	Hearing Loss
Izawa 2006	Met	GK	CR	20	(40)†	50	46, F	15 Min	Died
Chang 2004	AVM	NR	Cohort	12 - 20, 19.3	15 - 25, 24.1	80	NR, NR	30 Day	NR
Nataf 2004	AVM	LINAC	Cohort	19 - 28, 23	(27 - 56)	50 - 70, 70 (Median)	NR, NR	< 24 Hr	NR
Shin 2004	AVM	GK	Cohort	17 - 28, 20 (Median)	25 - 60, 40 (Median)	NR	NR, NR	< 30 Day	NR
Suzuki 2003	Met	LINAC	Cohort	20 - 25	NR	NR	NR, NR	1 Day	NR
							NR, NR	14 Day	NR
							NR, NR	14 Day	NR
							NR, NR	30 Day	NR
							NR, NR	30 Day	NR
Uchino 2003	Met	NR	CR	20	25 - 30	(67 - 80)†	44, F	2 Hr	Transient Aphasia
Shimizu 2001	AVM	GK	CR	20	40	50	50, M	29 Day	ND
Park 2000	Met	GK	CR	10	(20)†	50	69, M	3 Day	Died
Pollock 1994	AVM	GK	Cohort	15 - 25, 21	22.2 - 50, 36	≥50‡	35, F	30 Day	ND
							NR, NR	30 Day	ND
Colombo 1994	AVM	LINAC	Cohort	(13 – 36)†	18.7 - 40, 28.2	70 - 90	NR, NR	6 Day	NR

Dx=diagnosis; AVM=arteriovenous malformation; VS=vestibular schwannoma; Met=metastasis; GK=gamma knife; LINAC=linear accelerator; CR=case report; Cohort=retrospective observational cohort; Gy=gray; NR=not reported; ND=no deficit.
† Values in parenthesis were calculated from available data.
‡ 98% of patients were treated at ≥50% isodose line.

Table 1. Cases of hemorrhage within 30 days following stereotactic radiosurgery.

1998; Langer et al. 1998; Marks et al. 1990; Stefani et al. 2002; Turjman et al. 1995; Willinsky et al. 1988) are proposed risk factors that may have a confounded association with an increased risk of hemorrhage. Arteriovenous malformation size and location may be associated with hemorrhagic presentation and may not truly represent characteristics that increase the risk of AVM hemorrhage. Arteriovenous malformation size and location may also be associated with other AVM characteristics, such as feeding artery pressure and venous drainage pattern, respectively, that could independently predispose to AVM rupture. (Duong et al. 1998; Spetzler et al. 1992; Stefani et al. 2002)

Several studies provide evidence of independent risk factors for AVM hemorrhage. Deep venous drainage, (Kader et al. 1994; Langer et al. 1998; Duong et al. 1998; Marks et al. 1990; Mast et al. 1997) AVM size, (Kader et al. 1994; Langer et al. 1998) diffuse AVM morphology, (Pollock et al. 1996) feeding artery pressure, (Duong et al. 1998) intranidal aneurysms, (Marks et al. 1990) deep, periventricular or intraventricular AVM location, (Marks et al. 1990; Zipfel et al. 2004; Stefani et al. 2002) a single draining vein, (Pollock et al. 1996; Stefani et al. 2002) and venous ectasias (Stefani et al. 2002) have been shown to be independent risk factors. Studies also suggest other risk factors for AVM hemorrhage. Multiple aneurysms, (Turjman et al. 1995) perforating feeding vessels, (Turjman et al. 1995) and venous outflow compromise (Miyasaka et al. 1992; Vinuela et al. 1985) have been proposed to influence the risk of AVM hemorrhage.

There is additional evidence that a history of prior AVM hemorrhage predisposes to an increased risk of subsequent hemorrhage. (Crawford et al. 1986; Forster, Steiner, and Hakanson 1972; Fults and Kelly 1984; Graf, Perret, and Torner 1983; Halim et al. 2004; Itoyama et al. 1989; Kjellberg 1986; Mast et al. 1997; Pollock et al. 1996; da Costa et al. 2009) Studies have reported annual hemorrhage rates of 6% to 33% in the first year after a primary hemorrhage. (Forster, Steiner, and Hakanson 1972; Fults and Kelly 1984; Graf, Perret, and Torner 1983; Itoyama et al. 1989; Mast et al. 1997; da Costa et al. 2009) There is disagreement as to whether this risk remains elevated for the long term or only a short period following the initial hemorrhage, and some argue against the hypothesis that prior AVM hemorrhage increases the natural risk of subsequent hemorrhage. (Ondra et al. 1990; Stefani et al. 2002)

3. Risk factors for AVM hemorrhage – Radiosurgically treated AVMs

Since the first use of radiosurgery for AVM was reported in 1972, observational cohort studies have provided us with valuable information on rates of AVM rupture and risk factors associated with AVM hemorrhage during the latency period (Table 2). In one of the largest follow-up studies, the risk of AVM rupture during the latency period was reported to be 4. 8% per year during the first 2 years and 5. 0% per year for 3 to 5 years following SRS. (Pollock et al. 1996) Other studies report the risk to be 1. 2% to 6. 5% per year prior to obliteration. (Friedman et al. 1996; Friedman and Bova 1992; Karlsson, Lax, and Soderman 2001; Karlsson, Lindquist, and Steiner 1996; Maruyama et al. 2007; Miyawaki et al. 1999; Nataf et al. 2004; Nicolato et al. 2006; Pollock et al. 1994; Shin et al. 2004; Steiner et al. 1992)

The data from observational cohort studies have been used to propose risk factors associated with AVM hemorrhage after SRS. These studies have demonstrated that several of the risk factors for hemorrhage after SRS may be different from those associated with hemorrhage prior to treatment. The risk of AVM hemorrhage during the latency period is

Table 2. (Continued)

Author, (Yr)	Tx	Number Patients	Study Period	Prescription Dose (Gy) Range, Mean	Maximum Dose (Gy) Range, Mean	Isodose Line (%) Range, Mean	Follow-up Period (Months) Range, Mean	Latency Hemorrhage Number, (%)	Latency Hemorrhage Cumulative Incidence	Latency Period Annualized Hemorrhage Rate	Latency Hemorrhage Risk Factors****
Zabel-du Bois (2007)	LINAC	50	1996-2002	15-22, 18 (Median)	(18.75-27.5)	80	8.5-180, 37 (Median)	6 (12)	ND	ND	Obliteration status, AVM size, AVM volume, AVM score (RBAS), Dose†
Yen (2007)	GK	159	1970-2004	15-31, 22.5	22-90, 41.3	30-91, 50 (Median)	5-185, 59.4	1 (0.63)	ND	ND	ND
Moreno-Jimenez (2007)	LINAC	40	Jan 2003-Dec 2003	10.5-20, 15.4	13-22, 18.5	63-95, 84	23-34, 29	1 (2.5)	ND	ND	ND
Maruyama (2007)	GK	182	1990-2004	21	40.9	NR	NR	11 (6.0)	ND	2.0%	None†
Nicolato (2006)	GK	362**	Feb 1993-Dec 2004	16.8-43.3, 28.6	20-62.5, 40.5 (Median)	22-90, 54.2 (Median)	1.1-130.7, 30.6 (Median)	8 (2.7)	ND	1.2%	ND
Maruyama (2005)	GK	500	July 1990-June 2003	21	40.9	50	93.6 (Median)	23 (5.0)	ND	ND	ND
Zabel (2005)	LINAC	110	1998-2001	14-22, 18 (Median)	(17.5-27.5)	80	7.8-86, 30 (Median)	9 (8.2)	3.7% 1yr 3.0% 2yr 3.5% 3yr	ND	AVM size, Obliteration status†
Nataf (2004)	LINAC	756	Jan 1984-Dec 1999	19-28, 23	NR	50-70, 70 (Median)	0-178, 26	51 (6.7)	ND	3.1%	AVM size, SM grade, Reference isodose, Minimum dose, Intranidal/ paranidal aneurysm, Complete AVM coverage†
Shin (2004)	GK	400	June 1990-Nov 1999	17-28, 20 (Median)	25-60, 40 (Median)	NR	1-135, 63	21 (5.3)	4.6% 3yr 10.2% 5 yr 14.6% 10yr	1.9%	Age, AVM location, BA feeders, Cerebellar symptoms[A]
Zipfel (2004)	LINAC	268	NR	NR	NR	NR	NR	26 (9.7)	ND	ND	None†
Friedman (2003)	LINAC	269	Feb 1989-Feb 1999	NR	NR	NR	NR	28 (10)	ND	ND	None†
Inoue (2002)	GK	115	1991-1995	17-25, 20.1	NR	NR	NR	8 (7)	ND	ND	AVM flow rate[B]
Karlsson (2001)	GK	1593	1970-1995	NR	NR	NR	NR	56 (3.5)	ND	1.8%	Mimimum dose, Average dose, Age, AVM volume‡

Author, (Yr)	Tx	Number Patients	Study Period	Prescription Dose (Gy) Range, Mean	Maximum Dose (Gy) Range, Mean	Isodose Line (%) Range, Mean	Follow-up Period (Months) Range, Mean	Latency Hemorrhage Number, (%)	Latency Hemorrhage Cumulative Incidence	Latency Period Annualized Hemorrhage Rate	Latency Hemorrhage Risk Factors****
Miyawaki (1999)	LINAC	73	Mar 1988-Sept 1991	NR	17.5-46.5, 25 (Median)	23-90, 66 (Median)	NR	12 (16)	12%-16% 5yr 33%-55% 7yr	3.9%-5.5%	AVM size, venous drainage pattern, prior hemorrhage[C]
Pollock (1996)	GK	315	Aug 1987-Jan 1992	12-32, 20 (Median)	22-50, 35.7 (Median)	≥50***	47	21 (6.7)	ND	4.8%£ 5.0%ß	Unsecured proximal aneurysm[D]
Friedman (1996)	LINAC	201	May 1988-Feb 1995	15	NR	NR	NR	12 (6.0)	ND	4.8%€ 5.6%¥ 4.4%Æ	AVM volume, SM grade, Dose, Isodose line ≤70Gy[A]
Karlsson (1996)	GK	1604	Apr 1970-June 1992	NR	NR	NR	NR	49 (3.1)	ND	2.1%£	Minimum dose, Average dose, Age, AVM volume‡
Yamamoto (1995)	GK	121	Jan 1990-Dec 1993	16-22, 18	22-44, 35	50-70	12-60	7 (5.8)	ND	ND	None§
Pollock (1994)	GK	65	Aug 1987-Aug 1991	15-25, 21	22.2-50, 36	≥50***	24-60, 35	5 (7.7)	ND	3.7%	ND
Colombo (1994)	LINAC	180	Nov 1984-Apr 1992	NR	18.7-40, 28.2	70-90	1-88, 43.1	15 (8.3)	9.3% 1yr 13.3% 2yr	ND	Ratio maximum dose/peripheral dose[A]
Seifert (1994)	PB	68	Oct 1980-May 1990	NR	NR	NR	30-144	5 (7.9)	ND	ND	ND
Steiner (1992)	GK	247	Apr 1970-Dec 1983	NR	NR	NR	NR	9 (3.6)	3.4% 35mos 7.2% 2yr 11.2% 5yr	1.9%-6.5%	ND
Friedman (1992)	LINAC	80	May 1988-Aug 1991	10-25, 16.5	NR	70-90, 80	3-42, 19	2 (2.5)	ND	1.6%	ND
Lunsford (1991)	GK	227	Aug 1987-Aug 1990	12-27, 21.2	22-50, 36.5	40-90	3-36, 14	10 (4.4)	ND	ND	ND
Steinberg (1990)	PB	86	July 1983-Jan 1984	NR	NR	NR	24-72, 38	10 (12)	ND	ND	ND

AVM=arteriovenous malformation; Tx=treatment modality; LINAC=linear accelerator; GK=gamma knife; PB=proton beam; Gy-gray; NR=not reported; ND=not determined; RBAS=radiosurgery based AVM score; SM=Spetzler-Martin; BA=basilar artery.

**Separate analysis of patients age ≥21 years.

***98% of patients were treated at >=50% isodose line.

**** By univariate or multivariate analysis; † $p<0.05$; ‡ $p<0.01$; §=level of significance not reported.

𝒜=p<0. 05, level of significance not reported; ℬ=p=0. 005, level of significance not reported; 𝒞=p<0. 003, level of significance not reported; 𝒟 =p<0. 001, level of significance not reported.
£=per year during years 1-2; ß=per year during years 3-5; €=per year 1st year; ¥=per year 2nd year; Æ=per year during years 1-5.

Table 2. AVM hemorrhage during the latency period following stereotactic radiosurgery.

hypothesized to be related to patient age, (Karlsson, Lax, and Soderman 2001; Karlsson, Lindquist, and Steiner 1996; Shin et al. 2004) AVM size/volume, (Friedman et al. 1996; Karlsson, Lax, and Soderman 2001; Karlsson, Lindquist, and Steiner 1996; Miyawaki et al. 1999; Nataf et al. 2004; Zabel et al. 2005; Zabel-du Bois et al. 2007) and radiation dose. (Colombo et al. 1994; Friedman et al. 1996; Karlsson, Lax, and Soderman 2001; Karlsson, Lindquist, and Steiner 1996; Nataf et al. 2004; Zabel-du Bois et al. 2007) The presence of intranidal, paranidal, or unsecured proximal aneurysms, (Nataf et al. 2004; Pollock et al. 1996) AVM flow rate, (Inoue and Ohye 2002) and the extent of AVM coverage (Nataf et al. 2004) are also reported to be associated with the risk of post-radiosurgery AVM hemorrhage.

The use of observational cohort studies, whether prospective or retrospective, natural history or descriptive, to determine truly independent risk factors for AVM hemorrhage is inadequate for several reasons. Arteriovenous malformations are uncommon, thus the conclusions suggested by many observational studies are limited by small sample size. Selection bias cannot be avoided in studies of AVM natural history and risk factors for hemorrhage due to physician referral practices, surgeon treatment preferences and standards of care, and fatal hemorrhages excluding those patients from analysis. In addition, the clinical, morphological, and physiological characteristics of AVMs that are surgically resected differ from those that are treated with radiosurgery and those that are followed without treatment. The confounded association of risk factors for AVM hemorrhage can be addressed by statistical methods to control for confounding, but, even in well-designed observational studies, residual confounding will likely persist after statistical adjustment. Given the limitations of the retrospective observational cohort study design, it is unlikely that we will be able to estimate the true risk of AVM hemorrhage for a particular population. From these studies, though, the identification of factors that may be associated with AVM hemorrhage during the latency period has enhanced our understanding of the disease and influenced the evolution of radiosurgical treatment for AVM.

With so few literature reports of AVM hemorrhage in the early period following SRS, little is known of the risk factors for or mechanisms of AVM hemorrhage during the early period. To begin to understand the potential differences between AVM hemorrhage in the early period following SRS and AVM hemorrhage that occurs months to years following radiosurgery, it is important to understand the histological and ultrastructural effects of radiation in the central nervous system and the hemodynamic alterations that can occur in different pathophysiological settings. There is an acute inflammatory response following tissue irradiation, resulting in structural and functional vascular changes that can lead to vessel thrombosis and AVM rupture.

4. Histopathological effect of radiation and vessel obliteration

The tissue effects of radiation have been documented and studied since the discovery of ionizing x-rays. Both the desired outcomes and the undesired complications of any radiation

therapy are the result of the same pathophysiological processes in the irradiated tissue. The mechanisms of vascular obliteration after stereotactic radiosurgery are not completely understood, (O'Connor and Mayberg 2000) but several histological and ultrastructural studies have helped to elucidate the physiological basis. (Adams 1991; Chang et al. 1997; Schneider, Eberhard, and Steiner 1997; Szeifert et al. 1997; Szeifert, Major, and Kemeny 2005; Tu et al. 2006; Yamamoto et al. 1992) Focused irradiation causes damage to endothelial cells and induces the subsequent proliferation of smooth muscle cells, fibroblasts, and myofibroblasts in the subendothelial layer. The elaboration of collagenous extracellular matrix in the intimal layer follows, leading to progressive hyalinization and thickening of the intimal layer, stenosis of the irradiated vessels, and complete vessel occlusion and nidal obliteration.

The histological response of normal vessels to irradiation follows a predictable pattern, but the timing and extent of the response of both normal cerebral vessels to conventional irradiation and the abnormal vasculature of cerebral AVMs to radiosurgery is highly variable. (Fajardo and Berthrong 1988; Schneider, Eberhard, and Steiner 1997; Tu et al. 2006) A decrease in blood flow through AVMs, which is consistent with decreased luminal diameter due to intimal thickening, has been demonstrated on magnetic resonance (MR) imaging and angiography within a few months following radiosurgery. (Lunsford et al. 1991; Yamamoto et al. 1992) Arteriovenous malformations treated with radiosurgery may completely radiographically obliterate as early as a few months or more than 8 years after SRS, (Lunsford et al. 1991; Yen et al. 2007) and persistence of subtotal obliteration is documented during follow-up periods as great as 14 years after radiosurgery. (Yen et al. 2007) The vaso-occlusive effects of SRS, as demonstrated on MR imaging or angiography, progress slowly and heterogeneously, generally reaching a maximum at 1 to 3 years post-radiosurgery. Many studies have found that approximately 75% of AVMs are completely obliterated at 2 to 3 years post-radiosurgery. (Coffey, Nichols, and Shaw 1995; Guo et al. 1993; Lunsford et al. 1991; Shin et al. 2004; Yamamoto et al. 1993; Yamamoto et al. 1992) Observational studies utilizing MR imaging and angiography have documented the time course of the hemodynamic manifestations of vessel obliteration, (Quisling et al. 1991; Yamamoto et al. 1993) and the sequence of histological changes appears to correlate with the reduction in AVM size on imaging. (Schneider, Eberhard, and Steiner 1997) The true range of time to histological AVM obliteration, though, is unknown. There is evidence that radiographic obliteration does not correspond with histological obliteration. (Yamamoto et al. 1992) The difficulty in obtaining tissue during the early period following SRS results in a lack of histopathological studies of early AVM changes and a paucity of data concerning the time course of histological AVM obliteration.

Early radiation-induced obliteration of the venous system and resultant venous outflow impairment may increase the risk of early AVM hemorrhage following SRS, but there is a lack of literature evidence to support this hypothesis. There are no published ultrastructural or histopathological studies of AVMs in the early period following radiosurgery. Additionally, neither the histological effect of radiation on the venous drainage system of AVMs nor the variable radiosensitivity of the draining vessel walls compared to the nidus vessel walls has been explored. A case report of the histological findings at autopsy in a woman with an AVM treated with radiosurgery and confirmed by angiography to be obliterated at 2 years, who died of causes unrelated to the AVM, showed that obliteration occurs in nidal arteries before nidus-associated veins. (Yamamoto et al. 1995) Some studies

have demonstrated an increased resistance of veins to radiation-induced changes compared to capillaries and arteries. (Fajardo 1982) A study of SRS for treatment of venous angioma showed a lower proportion of complete or partial obliteration compared to radiosurgically treated AVMs receiving similar doses. (Lindquist et al. 1993) These observations suggest that the abnormal veins associated with vascular malformations may be less radiosensitive than arteries. The decreased radiosensitivity of veins and slower venous obliteration provide evidence against the role of radiation-induced vessel changes in AVM hemorrhage in the immediate post-radiosurgery setting. Based on the current knowledge of cellular responses to tissue irradiation, the time course of progressive intimal thickening and vessel occlusion, even if abnormally accelerated, cannot explain AVM hemorrhage in the early period following SRS.

5. Hemodynamic alterations and AVM hemorrhage

Venous thrombosis is a proposed mechanism for intracranial hemorrhage and there are reports in the literature of hemorrhage from venous malformations associated with thrombosis of the draining vein. (Field and Russell 1995; Merten et al. 1998; Yamamoto et al. 1989) In these reports, thrombus formation preceding hemorrhage is the hypothesized mechanism based upon the presence of thrombosis and hemorrhage on the same imaging study, but none of the reports provide pre-hemorrhage imaging studies demonstrating the temporal relationship of thrombosis and hemorrhage. Venous outflow obstruction due to venous thrombus formation is a mechanism for AVM hemorrhage following SRS. Physiologically, venous outflow impairment is believed to cause venous hypertension in a retrograde manner leading to elevated intranidal pressure and rupture of abnormal AVM vessels. (Garcia Monaco et al. 1990; Vinuela et al. 1985) Intraoperative measurements of pre-stenotic draining vein pressure in patients with segmental venous stenosis and a history of AVM hemorrhage have demonstrated venous hypertension. (Miyasaka et al. 1994) Several studies have identified characteristics of AVM venous drainage that may play a role in the pathophysiology of AVM rupture. Venous stenosis or occlusion impairing venous drainage, (Miyasaka et al. 1994; Miyasaka et al. 1992; Vinuela et al. 1985) the number of draining veins, (Albert 1982; Albert et al. 1990; Miyasaka et al. 1992; Pollock et al. 1996; Stefani et al. 2002) the location of draining veins as deep, superficial, or mixed, (Duong et al. 1998; Kader et al. 1994; Langer et al. 1998; Marks et al. 1990; Mast et al. 1997; Miyasaka et al. 1992; Turjman et al. 1995) and the presence of venous aneurysms or varices are the venous drainage characteristics reported to influence AVM hemorrhage. (Albert et al. 1990; Stefani et al. 2002)

In the setting of AVMs, the risk of rupture due to venous stenosis or occlusion and the resultant venous drainage impairment is debated. (Marks et al. 1990; Miyasaka et al. 1994; Miyasaka et al. 1992; Turjman et al. 1995; Vinuela et al. 1985; Willinsky et al. 1988; Young et al. 1994) While impaired venous drainage is viewed by some as an essential determinant of the hemodynamics of the AVM nidus, (Wilson and Hieshima 1993) limited work has been done to investigate the influence of altered hemodynamics due to venous outflow impairment on the risk of AVM hemorrhage. Biomathematical models based on electrical network analysis have been developed and used to theoretically investigate the hemodynamics within an AVM nidus. (Hademenos and Massoud 1996, 1996; Hademenos, Massoud, and Vinuela 1996; Hecht, Horton, and Kerber 1991; Lo 1993, 1993; Lo et al. 1991; Nagasawa et al. 1996; Ornstein et al. 1994) One study examined the development of

hyperperfusion during the AVM obliteration process and found that as AVM flow decreased during obliteration, feeding vessel pressure increased, draining vessel pressure decreased, and perfusion pressure in brain tissue surrounding the AVM increased. (Nagasawa et al. 1996) In another study of the theoretical risk of AVM rupture due to venous outflow obstruction, the investigators found that stenosis or occlusion of a high-flow draining vein was predictive of AVM rupture. (Hademenos and Massoud 1996)

Clinically, acute alteration in cerebral hemodynamics following surgical resection of an AVM is a known cause of postoperative hemorrhage. The risk of AVM hemorrhage due to acute alterations in hemodynamics is most commonly encountered in the setting of postoperative residual AVM. There is evidence suggesting that residual AVM is associated with early postoperative hemorrhage due to the persistence of high flow through a nidus with surgically impaired venous outflow. Hemodynamic changes following AVM resection are also theorized to play a causal role in neurological deterioration with or without hemorrhage or edema. Normal perfusion pressure breakthrough and occlusive hyperemia are two proposed hypotheses for neurological deterioration due to hemodynamic alterations following AVM resection. (al-Rodhan et al. 1993; Spetzler et al. 1978)

Occlusive hyperemia is a proposed hemodynamic mechanism for neurological decline following surgical removal of AVMs. (al-Rodhan et al. 1993) Based on angiographic findings in a group of patients who experienced neurological deterioration within 3 hours to 11 days following complete AVM resection, al-Rhodan and colleagues found that obstruction of the primary venous drainage or other venous structures accompanied by passive hyperemia was believed to be the cause of acute postoperative edema and/or hemorrhage in certain patients. Occlusive hyperemia in the setting of venous thrombosis has been proposed as a mechanism for neurological deterioration following radiosurgery for AVM. (Pollock 2000) Pollock provides radiographic evidence of acute draining vein thrombosis after radiosurgery in two patients with acute neurological deficits and hypothesizes that hemodynamic alterations occur in tissue surrounding the AVM after radiosurgery and lead to venous outflow impairment and perinidal edema that is manifest in neurological deficits. Pollock and colleagues propose that these changes are not due to radiation injury. Chapman and colleagues (Chapman, Ogilvy, and Loeffler 2004) provide further evidence supporting the hypothesis that venous occlusion and hyperemia may be one mechanism responsible for complications following radiosurgery. In their case report, they provide radiographic evidence of venous outflow impairment in two patients with acute neurological deficits developing months to years following SRS, and in one case offer the results of histological examination that failed to show radionecrosis.

Occlusive hyperemia in the postoperative setting can result in intracranial hemorrhage. Similarly, spontaneous venous thrombosis and venous hypertension may play a role in AVM hemorrhage following SRS. It is the opinion of some in the field that venous outflow restriction and resultant venous overload is a critical determinant of nidal and perinidal hemodynamics and often precedes AVM rupture. (Wilson and Hieshima 1993) Acute venous thrombus formation preceding intracranial hemorrhage is a physiologically sound mechanism for AVM hemorrhage, with radiographic support based on imaging of concurrent thrombus and hemorrhage. The authors of this chapter recently published radiographic documentation of an acute draining vein thrombus immediately preceding AVM hemorrhage and evidence of arterial inflow alterations (dilated internal carotid and

middle cerebral arteries) in the setting of venous outflow obstruction. Based on both the current understanding of the tissue effect of radiation and the evidence to support the hemodynamic alterations that link acute venous obstruction and intracranial hemorrhage, we postulate that one cause of AVM hemorrhage in the early period following radiosurgery may be acute venous thrombus formation, not due to early or accelerated radiation-induced changes that result in eventual vessel obliteration, but, rather, due to the acute inflammatory response of irradiated tissue.

6. Acute inflammatory response after radiation exposure

Radiation is a known stimulus for the acute inflammatory reaction, and vascular changes play a central role in the acute inflammatory response. Initiation of the acute inflammatory reaction results in the release of a variety of cytokines, especially thromboxane and prostaglandins, with vascular effects. Characteristic alterations in vessel caliber and endothelial permeability are hallmarks of the acute inflammatory response. (Acute and Chronic Inflammation 2005) Vasodilation and a leaky vasculature cause a slowing of blood flow and perivascular edema, and these hemodynamic changes may predispose to stasis and thrombus formation. Cytokine-mediated vascular changes and the hemodynamic consequences in various tissues, including the central nervous system (CNS), have been studied and the time course of pathogenic processes documented. (Nieder et al. 2002) Animal models of CNS irradiation have shown cytokine-mediated vascular changes resulting in vasodilation and endothelial permeability can occur within the first few hours after irradiation. (Siegal and Pfeffer 1995) The levels of vasoactive cytokines variably change in the weeks following irradiation with simultaneous increasing and decreasing levels of different cytokines resulting in phasic changes in vessel caliber and vascular permeability. (Mildenberger et al. 1990; Siegal and Pfeffer 1995; Siegal et al. 1996)

Functional vascular changes related to radiation-induced cytokine release are accompanied by structural alterations following irradiation. Endothelial cells are highly radiosensitive (Fajardo and Berthrong 1988) and even low doses of radiation can cause endothelial cell injury and death. Histopathological studies documenting endothelial cell death after irradiation have shown endothelial cell swelling leading to a narrowed vessel lumen followed by platelet and fibrin thrombi during the course of progressive capillary damage in an animal model. (Fajardo and Stewart 1973) Additional animal studies provide evidence for a dose-dependent reduction in the number of endothelial cells in rat CNS within one week following irradiation. (Hopewell et al. 1989) More recent studies have shown that endothelial cells in the CNS of mice undergo time- and dose-dependent apoptosis beginning within a few hours after irradiation. (Pena, Fuks, and Kolesnick 2000) Vessel smooth muscle cell atrophy is also a time- and dose-dependent phenomenon following irradiation. (Hopewell et al. 1989) With increasing radiation dose the severity of vascular damage in rat CNS increases while the latency decreases. (Kamiryo et al. 1996)

While highly radiosensitive, endothelial cells do not respond homogeneously after radiation exposure, (Brown, Farjardo, and Stewart 1973) and the response of the vasculature to radiation is not only time- and dose-dependent, but varies by tissue and vessel type. (Fajardo and Berthrong 1988) In human tissue, capillaries are the most sensitive to irradiation, while large arteries are less affected and medium-sized and large veins are even more resistant to radiation injury. Veins are generally radioresistant, but small veins in the

submucosa of the intestinal tract and the centrilobular veins of the liver have been shown to be susceptible to significant acute and chronic radiation injury, (Berthrong and Fajardo 1981; Fajardo and Colby 1980) demonstrating the variable tissue effect of irradiation.

Endothelial cell damage and functional changes of the vasculature can cause hemodynamic alterations that result in slowed blood flow and perivascular edema and predispose to stasis and thrombus formation. Independent of this pathway, whereby inflammation-induced vascular changes can lead to thrombosis, inflammation and thrombosis are directly linked. Specific cytokines, such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), are important mediators of both the inflammatory and coagulation pathways. Tumor necrosis factor is activated during the inflammatory process and functions to activate the inflammatory pathway. It also plays a role in initiation of the coagulation cascade. (Conway et al. 1989; Nawroth and Stern 1986; van der Poll et al. 1990) Interleukin-1 is another cytokine with pro-inflammatory and pro-coagulant effects. (Bevilacqua et al. 1986; Le and Vilcek 1987) In the central nervous system, animal studies of cytokine production after CNS irradiation provide evidence for radiation-induced production of TNF-α and IL-1 by microglia and astrocytes. (Chiang and McBride 1991; Hong et al. 1995; Merrill 1991) Models for the direct interactions between inflammation and thrombosis have been proposed to explain the association of endothelial injury, the inflammatory response, and thrombus formation. (Furie and Furie 1992; Stewart 1993)

Complications of the increased endothelial permeability and altered vessel caliber that characterize the acute inflammatory reaction following SRS are most commonly manifest through the development of vasogenic cerebral edema rather than thrombus formation. Vasogenic edema begins within hours after irradiation, but symptomatic edema may not be evident for days, or the edema may never become symptomatic. At our institution, this known acute complication of radiosurgery is treated prophylactically with the glucocorticoid dexamethasone beginning prior to SRS and continuing for 5 days following treatment. Corticosteroids function to reduce the manifestations of the acute inflammatory reaction by inhibiting the production of inflammatory mediators and reversing the permeability of the vascular endothelium. (Yamada K 1989; Hedley-Whyte and Hsu 1986; Jarden et al. 1989; Shapiro et al. 1990) Reduced endothelial permeability results in decreased tissue edema and improved microvascular circulation. (Hartman and Goode 1987; Zarem and Soderberg 1982)

The acute inflammatory response provides a mechanism for both direct and indirect thrombus formation following irradiation that could result in AVM rupture in the early period following SRS, and the variable response of vessels to radiation may explain the rare occurrence of AVM hemorrhage during the early period. Stereotactic radiosurgery can induce an acute inflammatory reaction in the AVM vessels that causes endothelial cell injury and vessel thrombosis. Due to the decreased radiosensitivity of veins, venous thrombosis and outflow obstruction resulting from radiation-induced acute inflammatory reaction is likely a rare event with clinical consequences that can range from none to edema and neurological deficits to devastating hemorrhage.

7. Conclusion

A risk of AVM hemorrhage following SRS persists during the latency interval. There is evidence on the role of inflammation in the pathophysiology of AVM rupture, and the

association between inflammation and AVM hemorrhage has been established. Arteriovenous malformation hemorrhage in the early period following radiosurgery may be related to the acute inflammatory response of irradiated vessels resulting in venous thrombus formation. There is an acute inflammatory response following tissue irradiation, resulting in structural and functional vascular changes that can lead to vessel thrombosis. The proposed mechanism of venous outflow obstruction leading to early AVM hemorrhage following radiosurgery is supported by laboratory evidence and suggested by clinical evidence. Radiographic evidence of the time course of thrombosis and hemorrhage supports the hypothesis that acute venous outflow obstruction immediately precedes AVM hemorrhage in this setting. The pathophysiology of AVM hemorrhage in the early period following SRS is different from that of AVM hemorrhage occurring months to years following radiosurgery.

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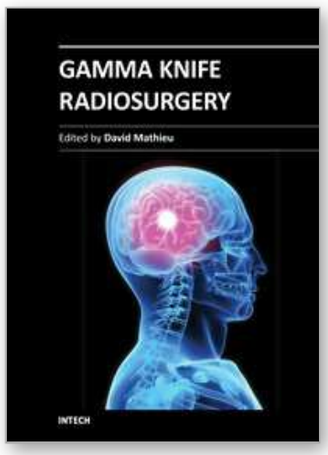
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Gamma knife radiosurgery is a minimally-invasive treatment alternative for intracranial disorders, including tumors, vascular malformations, facial pain and epilepsy. This book will allow the reader to learn when gamma knife radiosurgery is appropriate and what to expect as treatment results.

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