TESIS DOCTORAL

RADIOCIRUGÍA ESTEREOTÁXICA EN EL TRATAMIENTO DE MALFORMACIONES ARTERIOVENOSAS CEREBRALES

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SUMARIO:

1. INTRODUCCIÓN

Las malformaciones arteriovenosas cerebrales (MAV) son anomalías congénitas del cerebro en las que el flujo arterial llega directamente a una vena sin pasar por la red de capilares. La frecuencia estimada de su aparición es de ≈1 por 100000 personas y año [1]. La manifestación más frecuente y nefasta de una MAV cerebral es el sangrado intracraneal [2]. Los estudios sobre la historia natural de estas malformaciones calculan que la tasa de hemorragia anual se acerca al 2-4% [3,4], lo cual significa que la mayoría de las MAV detectadas en la edad joven sangrarán a lo largo de la vida del paciente. La morbilidad de una hemorragia intracraneal por MAV supera el 10%, y la morbilidad se acerca al 50%. El tratamiento va encaminado principalmente a la prevención de esta complicación, y puede ser quirúrgico, endovascular o radioterápico. Otras manifestaciones descritas de las MAV cerebrales incluyen crisis epilépticas, cefaleas (una presentación clínica frecuente es la migraña con aura) o síntomas focales.

Al existir múltiples síntomas de presentación y múltiples opciones terapéuticas, esta patología precisa idealmente de un equipo multidisciplinar que abarque la neurología, la neurocirugía, la radiología intervencionista y la radioterapia [5]. Esto todavía no se da en muchos centros hospitalarios, donde las MAV son controladas por especialistas únicos (neurólogo o neurocirujano). Aquellos pacientes que precisan un tratamiento radioterápico son en muchas ocasiones derivados a centros privados y pierden el seguimiento con su especialista habitual. Estas condiciones hacen que reunir un grupo de pacientes homogéneo y bien controlado sea un reto, y explica en parte la falta de estudios que existen sobre este tema.

El presente trabajo de doctorado se centra, como su nombre indica, en la radiocirugía (RC) estereotáxica aplicada a la terapia de las MAV. La radiocirugía es un método no invasivo que consiste en la aplicación de una única sesión radiación (con frecuencia rayos gamma, el así llamado Gamma Knife) sobre el nido de la MAV. Pocas veces es usada en solitario, ya que típicamente es aplicada en conjunción con la embolización [6], consiguiendo entre ambas una tasa de erradicación completa de las MAVs de un 70% [7].

Resulta especialmente útil para tratar MAV cerebrales inaccesibles quirúrgicamente por ser demasiado profundas, grandes o localizadas en áreas elocuentes del cerebro. A diferencia de la neurocirugía, cuyos efectos son inmediatos, su aplicación conlleva una lenta oclusión del nido a medida que las células endoteliales de los vasos irradiados proliferan y lo taponan [8]. Esta eficacia tardía (hasta 3 años, en los que el paciente permanece expuesto al riesgo teórico de un sangrado intracerebral) [9] y una serie de complicaciones propias de la irradiación, hacen que la validez de la radiocirugía a la hora del tratamiento de ciertos tipos de MAV sea aún controvertida. En especial no está bien documentada su efectividad en la prevención de sangrados en MAV no hemorrágicas, o sea aquellas que aún no han presentado sangrado intracraneal en el momento del diagnóstico. En esos casos algunos especialistas abogan por tratamientos conservadores [10], ya que no existen suficientes estudios que demuestren que la radiocirugía disminuya el teórico riesgo futuro de rotura y sangrado. Tampoco están bien documentadas las posibles complicaciones específicas de este tratamiento a medio y largo plazo.

El estudio presentado en este trabajo de doctorado fue diseñado para dar respuesta a algunas de las preguntas arriba planteadas. Se trata de un estudio observacional realizado sobre una cohorte de pacientes con malformaciones arteriovenosas cerebrales seguidos en el hospital Universitario la Fe de Valencia (incluyendo las Unidades de Neurología, Neurocirugía y Neuropediatría) antes y después de ser tratados con radiocirugía. Se recogieron datos de 108 pacientes, un número muy amplio dadas las características muy específicas del grupo, que fueron evaluados durante una media de 25 meses antes y 65 meses después del tratamiento.

2. ESTADO DEL TEMA Y OBJETIVOS:

Existen dos aspectos especialmente relevantes en lo que al tratamiento de las MAV mediante la radiocirugía se refiere: el primero es la indicación de dicho tratamiento con el fin de prevenir la hemorragia cerebral, y el segundo es la probabilidad de complicaciones tardías debidas a éste. Dado el efecto diferido de la radiocirugía, todavía no está del todo probado que sea eficaz en disminuir las tasas de hemorragia intracraneal en MAVs que no han presentado sangrado en el momento de su diagnóstico, y que por tanto pueden tener una menor probabilidad de hacerlo en el seguimiento. De hecho, existe controversia sobre las indicaciones de tratamiento de estas malformaciones "silentes". El único estudio aleatorizado que se ha ocupado del tratamiento de malformaciones, el ARUBA, se puso en marcha en 2007 con el fin de reclutar 800 pacientes con MAV no hemorrágicas a tratamiento intervencionista de cualquier tipo (cirugía, embolización o RC) o conservador [10]. El estudio se ha encontrado desde el principio rodeado de polémica por su mensaje no-intervencionista [11]. Fue parado en 2013 tras incluir unos 223 pacientes al demostrarse en el análisis intermedio una tasa de muerte y/o ictus claramente superior en el brazo intervencionista (10% vs 33%, con un tiempo medio de observación de 3 años) [12]. Sin embargo, al no hacer distinción entre diferentes tipos de tratamientos intervencionistas (permitía la elección de la "mejor opción" individualizada para cada caso) no ha arrojado suficiente información sobre la radiocirugía en particular para el tratamiento de las MAV.

A diferencia de la microcirugía y la embolización, que son técnicas invasivas con cierta morbimortalidad periprocedural, la RC ofrece una mínima tasa de complicaciones inmediatas. Por otro lado, dado que se aplica en una población mayoritariamente joven, las complicaciones tardías cobran un significado especial en la evaluación de su idoneidad. Se han descrito cambios de imagen en resonancia magnética (RM) hasta 10 años tras la terapia, desde roturas de barrera hematoencefálica hasta edemas extensos, llegando a necrosis [13-15]. Algunos pacientes permanecen asintomáticos a pesar de llamativas alteraciones en resonancia, mientras que otros pueden presentar clínica de nueva aparición más grave que la ocasionada por la propia malformación [16].

Teniendo en cuenta lo arriba referido, los objetivos concretos del estudio fueron:

Objetivo 1:

a) Calcular las tasas de hemorragia en pacientes con MAV tratadas con RC, tanto con sangrado previo como sin él, en diferentes momentos de tiempo.

b) Valorar los factores de riesgo que se asocian a las hemorragias.

Los resultados fueron publicados en el artículo Postradiosurgery hemorrage rates of arteriovenous malformations of the brain: influencing factors and evolution with time. *Stroke*; 2012;43:1247-1252, presentado más adelante como Artículo 1.

Objetivo 2:

a) Calcular la tasa de complicaciones radiológicas a largo plazo provocadas por la radiocirugía

b) Definir los factores contribuyentes a dichas complicaciones.

Los resultados fueron publicados en el artículo Late clinical and radiological complications of stereotactical radiosurgery of arteriovenous malformations of the brain, Neuroradiology 2013;55:405-412, presentado como Artículo 2.

Las dos publicaciones definen todos los aspectos del estudio realizado y se complementan perfectamente, siendo por tanto ideales para ser presentadas en forma de tesis doctoral por artículos.

3. PACIENTES Y MÉTODOS:

3.1. CARACTERÍSTICAS DEL GRUPO:

El estudio se realizó de manera retrospectiva sobre una serie de pacientes consecutivos con MAV tratados con radiocirugía y seguidos en el Hospital Universitario La Fe de Valencia desde 1994 hasta 2010. Los criterios de indicación de la radiocirugía en este grupo fueron, típicamente, MAVs localizadas en zonas profundas y/o elocuentes que las hacían inabordables quirúrgicamente. En muchos casos, han recibido tratamiento coadyuvante endovascular previo para disminuir el tamaño del nido.

Se revisaron las historias clínicas de los pacientes. Aquellas personas que habían perdido el seguimiento fueron avisadas para volver a la consulta para una nueva revisión. Se recogieron los datos demográficos y los factores de riesgo vascular, así como los datos referentes a la malformación (localización, tamaño, gradación Spetzler-Martin, drenaje venoso, presencia de aneurismas etc) y a la radiocirugía (dosis total, isodosis, número de focos, número de radiocirugías etc). En cuanto a la forma de presentación, las MAV fueron clasificadas en hemorrágicas y no-hemorrágicas. Estas últimas fueron además subclasificadas según hayan presentado crisis, cefalea, síntomas focales o hayan sido completamente asintomáticas. En general, para la descripción de las MAV se usaron los criterios propuestos para tal fin por *Atkinson et al* [17].

El estudio contó con el visto bueno del Comité Ético del Hospital Universitario La Fe de Valencia.

3.2. RADIOCIRUGÍA:

Las radiocirugías se realizaron en una sesión única usando cuchillo Gamma con ayuda de un aparato estereotáctico Leskell y simulación virtual basada en RM y arteriografía en la Clínica Virgen del Consuelo de Valencia. El protocolo consistió en usar dosis de 18 Gy en la isodosis de 80% ajustada al margen del nido.

3.3. SEGUIMIENTO:

El seguimiento de estos pacientes fue, por protocolo de nuestro hospital, semestral hasta un año después de la radiocirugía, y anual posteriormente. Se realizó una RM cerebral con contraste previamente a cada visita clínica. En caso de aparición de nuevos síntomas o empeoramiento de déficits preexistentes se realizó además una tomografía computerizada (TC) urgente seguida de una RM. Aproximadamente tres años tras el tratamiento se realizó una arteriografía de control con el fin de valorar el cierre de la MAV, a no ser que el nido se viera claramente patente en otras pruebas de imagen. Si 4 años tras el procedimiento la MAV seguía abierta, se planteaba una segunda radiocirugía.

Aquellos pacientes que a la hora de realizar el presente estudio habían perdido ya el seguimiento en nuestro hospital (más de 2 años desde la última visita) fueron avisados telefónicamente para acudir nuevamente a la consulta. A todos se les realizó una nueva RM y una visita clínica donde se completaron los datos necesarios para el estudio.

3.4. VALORACIÓN RADIOLÓGICA:

Para la valoración de las complicaciones propias de la radiocirugía se revisaron las resonancias anuales de los pacientes en busca de los hallazgos típicos. Esta parte del estudio fue realizada por dos radiólogos expertos ciegos respecto a las características clínicas de los pacientes. Se anotó la presencia de edema (brillo en secuencias T2 o Flair), rotura de la barrera hematoencefálica o BHE (captación de contraste en secuencias T1) y necrosis (hipointensidad en secuencias T1, captación de contraste circular y/o formación de quistes). Los hallazgos fueron puntuados en una escala semicuantitativa propuesta por *Levergrün et al* [13], clasificándose las lesiones en mínimas, perilesionales, moderadas (menos de ¼ de la superficie del corte) y graves (más de 1/4). Un ejemplo de la clasificación puede encontrarse en la Figura 1 del Artículo 2.

En cuanto al sangrado, se definió como aparición brusca de una clínica compatible y de una imagen nueva sugerente de sangrado en TC o RM.

3.5. VALORACIÓN CLÍNICA:

Diagnósticos clínicos de interés fueron la hipertensión intracraneal (definida mediante una clínica, una exploración neurológica y un examen oftalmoscópico compatible), desarrollo de déficits neurológicos nuevos o empeoramiento claro de los preexistentes, hemorragias intracerebrales o crisis epilépticas de nueva aparición.

3.6. MÉTODO ESTADÍSTICO:

Se usó media con desviación típica y/o porcentajes para la presentación de las diferentes variables, o la mediana con el rango intercuartílico en el caso de que la distribución no fuera normal. Se usaron análisis univariantes (chi cuadrado, t-test) para calcular la relación de las diferentes variables entre sí. $P<0.05$ fue considerado como de significación estadística. Finalmente, se realizaron análisis multivariantes en el que se incluyeron las variables significativas de los

análisis anteriores. Así mismo, se calcularon las curvas de supervivencia de Kaplan Meier y los log rank correcpondientes.

Para el cálculo de las tasas de hemorragia se anotó la aparición de esta complicación junto con la fecha. Las tasas propiamente dichas se calcularon como el número de eventos durante un tiempo predefinido, dividido por el sumatorio de la duración de los períodos individuales de todos los pacientes, de forma similar a la utilizada en otras publicaciones [18]. Definimos 4 intervalos de tiempo: antes del diagnóstico, desde el diagnóstico hasta la RC, 3 primeros años tras las RC (período de latencia) y pasados los 3 años desde la RC. Se realizaron cálculos separados dependiendo de si la presentación de la MAV fue hemorrágica o no hemorrágica. A la hora de calcular las tasas de sangrado pre-diagnóstico, se asumió que las MAV han estado presentes en el cerebro de los pacientes desde su nacimiento y que éstos han estado por tanto en riesgo de sangrado durante toda su vida. Este es el método habitual utilizado en otros estudios para este fin [19,20].

Postradiosurgery Hemorrhage Rates of Arteriovenous Malformations of the Brain

Influencing Factors and Evolution With Time

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Background and Purpose—The long-term benefit of radiosurgery of brain arteriovenous malformations (AVM), especially nonhemorrhagic cases, is controversial. We calculated hemorrhage rates pre- and posttreatment and analyzed the risk factors for bleeding based on cases followed at our site.

Methods—One hundred eight patients, age 36±17 years, 56 men. The mean follow-up was 65±44 months (median, 54; interquartile range, 33–94). Most AVMs were small (74.1% <3 cm in diameter); 48.1% were located in an eloquent area, 27.8% had deep drainage, and 39.8% presented with hemorrhage.

Results—The annual hemorrhage rate for any undiagnosed AVM was 1.2%, and 3.3% for AVMs with hemorrhagic presentation. Older patients, cortical or subcortical AVMs, and cases with multiple draining veins were less likely to present with bleeding. During the first 36 months postradiosurgery, hemorrhagic AVMs had a rebleeding rate of 2.1%, and a rate of 1.1% from 3 years onwards. Nonhemorrhagic AVMs had a hemorrhage rate of 1.4% during the first 3 years and 0.3% afterward. Arterial hypertension and nidus volume were independent predictors of bleeding after treatment. Mean nidus obliteration time was 37±18 months (median, 32; interquartile range, 25–40), with hemorrhage rate of 1.3% before and 0.6% after obliteration, and 1.9% for AVMs that were not closed at the end of follow-up.

Conclusions—Both hemorrhagic and nonhemorrhagic AVMs benefit from radiosurgical therapy, with gradual decrease in their bleeding rates over the years. Albeit small, the risk of hemorrhage persists during the entirety of follow-up, being higher for cases with hemorrhagic presentation and nonobliterated AVM. **(*Stroke*. 2012;43:1247-1252.)**

Key Words: brain arteriovenous malformation ■ radiosurgery ■ bleeding rate ■ occlusion

Radiosurgery (RS) is a noninvasive method for treating surgically inaccessible brain arteriovenous malformations (AVM), based on proliferation of irradiated endothelial cells and progressive occlusion of the nidus. Its delayed efficacy and potential long-term side effects make the unbiased evaluation of its validity in preventing cerebral hemorrhages difficult. This is especially true in regards to radiosurgical treatment of nonruptured AVM, where controversy exists concerning different management alternatives. Although many centers use the same approach with unruptured AVMs as with hemorrhagic cases (surgery, RS, or embolization) to diminish their lifelong risk of first bleeding, others advocate for less aggressive behavior, to the point of no treatment.[1,2]

Our study analyzes bleeding rates and risk factors for hemorrhage in patients treated with RS, the aim being to evaluate the usefulness of this technique in preventing cerebral bleeds in both ruptured and nonruptured brain AVM.

Patients and Methods

Patients

This study comprises a series of consecutive patients with brain AVM followed at our site since 1994. Though the referral criteria for RS varied on an individual basis, general indications were small AVMs located in deep or eloquent areas of the brain (sensorimotor, language, visual, thalamus, hypothalamus, internal capsule, brain stem, cerebellar peduncles, and deep cerebellar nuclei) that made them unsuitable for surgery. In many cases, embolizations were performed before the RS to decrease nidus diameter. Briefly, catheterization was performed under general anesthesia with transfemoral approach by using standard coaxial techniques. Guiding catheter was located in carotid or vertebral artery, and a microcatheter was navigated to the nidus of the AVM. Once the tip was in the desired position, injection of embolization material was carried out. Until 2007, NBCA and lipiodol with Magic catheter (Balt) was used. After 2007, Onix with Marathon (ev3), UltraFlow (ev3), or Sonic (Balt) catheter was used according to standard embolization technique.[3] Typically, several sessions were completed before the patient was referred to RS. Very occasionally, patients underwent RS after a surgical procedure.

Demographic data and presence of cardiovascular risk factors were documented. Arterial hypertension was defined as repeatedly

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elevated blood pressure exceeding 140/90 mm Hg, or as use of antihypertensive drugs. Current smoking habits were also noted. Nidus characteristics (size, location, drainage, presence of aneurisms) as seen on diagnostic digital angiography and brain magnetic resonance (MR) were all recorded according to published standards.[4]

For the purpose of this study, AVMs were classified as hemorrhagic or nonhemorrhagic based on their presentation. Hemorrhagic AVM were defined as having radiological signs of acute bleeding on computed tomography (CT) scan or MR together with compatible clinical symptoms. Nonhemorrhagic AVMs had no such signs, and were subsequently subclassified as having presented with epileptic seizures, headaches, focal symptoms, or none of the above.

This study was approved by the hospital ethics committee.

Radiosurgery Technique

Stereotactic RS was performed in a single session with the use of Gamma knife. A Leksell stereotaxic frame was affixed to the patient′s head (Elekta AB). Virtual simulation and planification were performed based on MR and digital arteriography. Per protocol, a dose of 18 Gy was applied to the 80% isodose line encompassing the margin of the nidus.

Follow-Up

Patients were followed biannually from the moment of diagnosis up until 1 year postradiosurgery, and annually afterward. Serialized contrast enhanced MR studies were performed annually, and also if the patient complained of new or worsening symptoms. Digital arteriography was scheduled 3 years after RS, unless a previous MR clearly showed the persistence of anomalous vessels or a patient refused the procedure. Nidus obliteration was defined based on angiographic criteria: absence of abnormal vessels in the area of the nidus, normalization of the draining veins and normal circulation time.[5] If the malformation was still patent on MR or angiography after 4 years, the possibility of a second RS was explored. At any time during the follow-up, newly acquired symptoms warranted an urgent CT and a scheduled MR. Hemorrhage was defined as any clinically relevant event with fresh blood in the vicinity of the malformation confirmed through CT or MR.

Statistical Analysis

Hemorrhage rates were calculated as the number of events during a predefined period divided by the sum of the duration of individual observation periods. We performed the calculations for birth-to-diagnosis, diagnosis-to-RS, and postradiosurgery time periods. To calculate birth-to-diagnosis bleeding rates, we assumed that patients were at risk for hemorrhage from the moment of their births.[6,7] For the diagnosis-to-RS and postradiosurgery bleeding rates, we performed separate analysis for hemorrhagic and nonhemorrhagic subgroups. Last, for the postradiosurgery analysis, we calculated the hemorrhagic rates during and after a predefined period of 3 years to correct for the delayed effect of treatment. Three years is a widely accepted postradiosurgery waiting period in many centers, including ours, after which other treatment options are often explored.

For analysis of the effect of nidus obliteration on the bleeding risk, we encountered the same problem as all studies on RS of AVMs do. The exact moment of nidus closure is unknown. Other authors have attempted to infer the moment of nidus closure from serialized MRs (defining it as the midpoint between the dates of the last images showing a patent nidus and the first images suggesting AVM closure). The problem with this approach is that MR angiography has lower spatial and temporal resolution than does digital angiography, and can easily miss residual slow, small-flow shunts. Conversely, perinidal contrast uptake may not represent patent residual vessels, but rather a localized brain-blood barrier disruption caused by RS.[8,9] Therefore, we considered the MR-based nidus closure dates to be insufficiently precise, and preferred to use the date of negative digital angiography as the moment of confirmed AVM closure. We felt that this approach was both more precise and more similar to clinical practice (where digital angiography is always necessary to confirm definitively the closure), even if it could result in longer observation periods and, therefore, lower hemorrhagic rates during the latency period.

Univariate tests (χ^2, t test) and multivariate logistic regression analysis were used to describe the association of demographic and clinical variables and nidus characteristics with the initial hemorrhagic presentation of the AVM. Kaplan-Meier survival curves, together with log-rank tests, were used to represent the evolution of hemorrhagic and nonhemorrhagic cohorts in time. Univariate and multivariate Cox regression hazard models were used to test for risk factors for hemorrhage during follow-up. Patients were censored at first postradiosurgical hemorrhage, if they underwent another treatment (microsurgery or second radiosurgery), were lost to follow-up, or died. Data are reported as mean±SD, median, and interquartile range. Hazard ratios with 95% CIs are presented. $P<0.05$ is considered to be statistically significant.

Results

General Patient Characteristics

A total of 108 cases were included in the study. Mean age at diagnosis was 36 years (range, 4–73 years), and 55% were men. There were 12 children younger than age 18 years. Patient demographics and medical history, radiological characteristics of AVM (location, size, Spetzler-Martin scale, aneurisms, and drainage), as well as details of other treatments undergone before RS are presented in Table 1. The same table also lists the presentation symptoms of nonhemorrhagic AVMs.

Forty-three patients presented with hemorrhage, and 3 of them had a second bleeding event before the diagnosis was made. The Kaplan-Meier curve representing hemorrhages of undiagnosed AVMs is shown in Figure 1.

Hemorrhage Rates Before Diagnosis

Assuming that patients were at risk for hemorrhage since their birth, their collective time at risk amounted to 3909 years. The annual hemorrhage rate for any undiagnosed AVM was 1.2%. The hemorrhage rate for AVMs that had presented with a hemorrhage was 3.3% (46 events in 1397 risk-years).

Age, location of the nidus, single draining vein, and exclusively deep drainage were associated with hemorrhagic presentation on univariate analysis. Older patients and cortically or subcortically located AVM were less likely to have presented with bleeding. On multivariate analysis, the first 3 factors retained their influence on the likelihood of initial hemorrhagic presentation (Table 2).

Hemorrhage Rates Between Diagnosis and Radiosurgery

Mean time between diagnosis and radiosurgery was 25±49 months (median, 11; interquartile range, 2–27). In 69 cases (64%), embolizations were performed before the RS (median of 3 sessions). Four patients underwent surgery. Three interventions happened more than 10 years before RS (2 were presumably successful, but persistence of nidus was discovered during follow-up, and 1 failed to remove the AVM). One patient underwent evacuation of a brain hematoma.

Seven additional bleedings were registered. Four of them were rebleedings. Annual rebleeding rate in hemorrhagic AVMs was 3.8% (4 cases in 1276 risk-months). Nonhemorrhagic AVMs had an annual bleeding rate of 2.6% (3 events in 1401 risk-months). Figure 2A presents survival curves for this period (log-rank, 0.22).

Table 1. General Patients and AVM Characteristics

Age at diagnosis (y)	36+/−17
Men/women	56/52
Previous medical history	
Smoking	28 (25.9%)
Hypertension	11 (10.2%)
Presenting symptoms	
Hemorrhage	43 (39.8%)
Seizure	35 (32.4%)
Headache	17 (15.7%)
Neurological deficit	2 (1.9%)
Other	11 (10.2%)
Spetzler-Martin scale (items)	
Size <3 cm	80 (74.1%)
Size 3–6 cm	22 (20.3%)
Size >6 cm	6 (4.6%)
Eloquent area	52 (48.1%)
Deep drainage	30 (27.8%)
Sperzler-Martin scale (points)	
1	36 (33.3%)
2	38 (35.2%)
3	26 (24.1%)
4	8 (7.4%)
Location	
Cortico-subcortical	78 (72.2%)
Other	30 (27.8%)
Ventricular	6
Basal ganglia	8
Cerebellum	13
Brain stem	3
Parietal	14 (12.8%)
Occipital	12 (11%)
Frontal	30 (27.5%)
Temporal	26 (23.9%)
Mean nidus volume (cm^3)	5.8+/−11
Percentile 25	0.5
Percentile 50	2.0
Percentile 75	5.5
Other treatments before radiosurgery	
Microsurgery	4 (3.7%)
Embolization	69 (63.9%)
Aneurysms	17 (15.7%)
Drainage	
Deep only	21 (19.4%)
Superficial only	57 (52.3%)
Single draining vein	45 (41.3%)
Embolization	69 (64%)
Second radiosurgery	20 (18.5%)

AVM indicates arteriovenous malformations.

Hemorrhage Rates After Radiosurgery

There were 6 new bleeds during a mean observation period of 65±44 months (median, 54; interquartile range, 33–94). Twenty patients underwent second radiosurgery after the initial 1 failed to obliterate the nidus. Two underwent a microsurgery. Four patients died, 2 of them from cerebral hemorrhage.

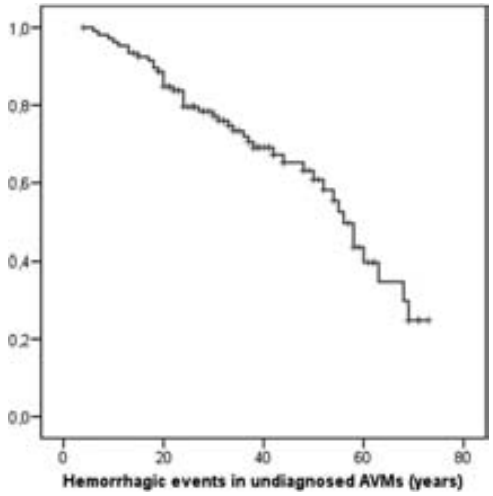

Figure 1. Kaplan-Meier survival curve for hemorrhages of undiagnosed AVMs (birth-to-diagnosis period).

The cohort of patients with hemorrhagic AVM had an annual rebleeding rate of 2.1% during the first 3 years after radiosurgery (2 cases in 1113 risk-months). After the initial 3 years, the rate was reduced to 1.1% per year (1 case in 1060 risk-months). Patients with nonhemorrhagic presentation had an annual hemorrhage rate of 1.4% during the first 3 years (2 cases in 1683 risk-months), and 0.3% afterward (1 in 3582 risk-months). Kaplan-Meier curves are presented in Figure 2B (log-rank, 0.53). The overall evolution of the bleeding rates is summarized in Table 3.

Influence of AVM Closure on the Hemorrhage Rate

There were 3 hemorrhagic events among the 52 patients with angiographic evidence of nidus obliteration. Mean time between radiosurgery and confirmation of closure was 37±18 months (median, 32; interquartile range, 25–40). Before the obliteration was confirmed, the annual hemorrhage rate was 1.3%. After the obliteration of the nidus, the rate decreased to 0.6% (1 case in 2034 risk-months).

As for AVMs that did not have conclusive evidence of nidus closure at the end of follow-up, their annual hemorrhage rate was 1.9% (3 events in 1843 risk-months).

Factors Influencing Postradiosurgical Hemorrhage

Smoking and arterial hypertension were independent risk factors in univariate analysis, increasing the postradiosurgical bleeding risk more than 2-fold and 4-fold, respectively. Diameter of less than 3 cm, smaller AVM volume, Spetzler-Martin scale of 1 or 2, and absence of aneurisms were protective factors. When entered in a multivariate model, only hypertension, diameter, and aneurisms retained their significance (Table 4).

Discussion

Postradiosurgical Bleeding Risk of Hemorrhagic and Nonhemorrhagic AVM: Does 1 Therapy Benefit All?

It is known that radiosurgery obliterates 70% to 90% of brain AVM after a latency period of about 3 years.[10] The expecta-

Table 2. Univariate and Multivariate Logistic Regression Analysis of the Pretreatment Bleeding Risk Factors

	Univariate Analysis			Multivariate Analysis		
	Hazard Ratio	95% CI	*P* Value	Hazard Ratio	95% CI	*P* Value
Age at diagnosis (decades)	0.784	0.784–0.994	0.044*	776	0.609–0.991	0.043*
Men	1.115	0.515–2.415	0.782			
Previous medical history						
Smoking	0.971	0.402–2.342	0.947			
Hypertension	0.850	0.233–3.096	0.805			
Spetzler-Martin scale (items)						
Size <3 cm	0.890	0.365–2.174	0.799			
Eloquent area	1.047	0.484–2.262	0.907			
Deep drainage	1.312	0.548–3.135	0.541			
Cortico-subcortical AVM	0.380	0.158–0.921	0.032*	0.371	0.152–0.917	0.036*
Nidus volume (cm^3)	1.037	0.991–1.085	0.131			
Aneurysms	1.033	0.357–2.989	0.952			
Exclusively deep drainage	3.086	1.152–8.264	0.025*	2.242	0.705–7.143	0.171
Single draining vein	5.988	2.439–14.706	0.001*	5.650	2.033–15.625	0.001*

AVM indicates arteriovenous malformations.
*$P<0.05$.

tion behind this treatment is that obliterating the malformation will decrease its risk of cerebral hemorrhage; but, in reality, the effect of radiotherapy on the bleeding rate has not been proven to be universally positive.[11] Latest series attest to the fact that radiosurgery does lower the overall hemorrhage risk of unselected AVM, but the conclusions are less clear-cut when it comes to exclusively nonhemorrhagic cases. A retrospective observational study of 500 patients by Maruyama et al revealed an overall decrease in the hazard ratio for bleeding by 54% during the latency period and by 88% after the latency period (when compared with the diagnosis-to-radiosurgery period). The decrease was greater for hemorrhagic AVM. For nonhemorrhagic AVM, there was a decreasing trend that did not reach statistical significance.[12]

A recent study of Yen et al, who reviewed 1204 patients treated with gamma knife, provides even more comprehensive data.[13] In the hemorrhagic AVM subgroup, the rebleeding rate was 10.4% during the diagnosis-to-treatment period and 2.8% during the latency period. In the nonhemorrhagic subgroup, the bleeding rates were 3.9% and 2.2%, respectively.

Our own data also show a progressive decrease in bleeding rates: from 3.8% before treatment, to 2.1% during latency period, to 1.1% after latency period for the hemorrhagic subgroup, and from 2.6% to 1.4% to 0.3% for the nonhemorrhagic subgroup, respectively.

One must remember, though, that preradiosurgery bleeding rates do not equal natural, untreated bleeding rates. In our series, as well as in most other studies, AVMs were fre-

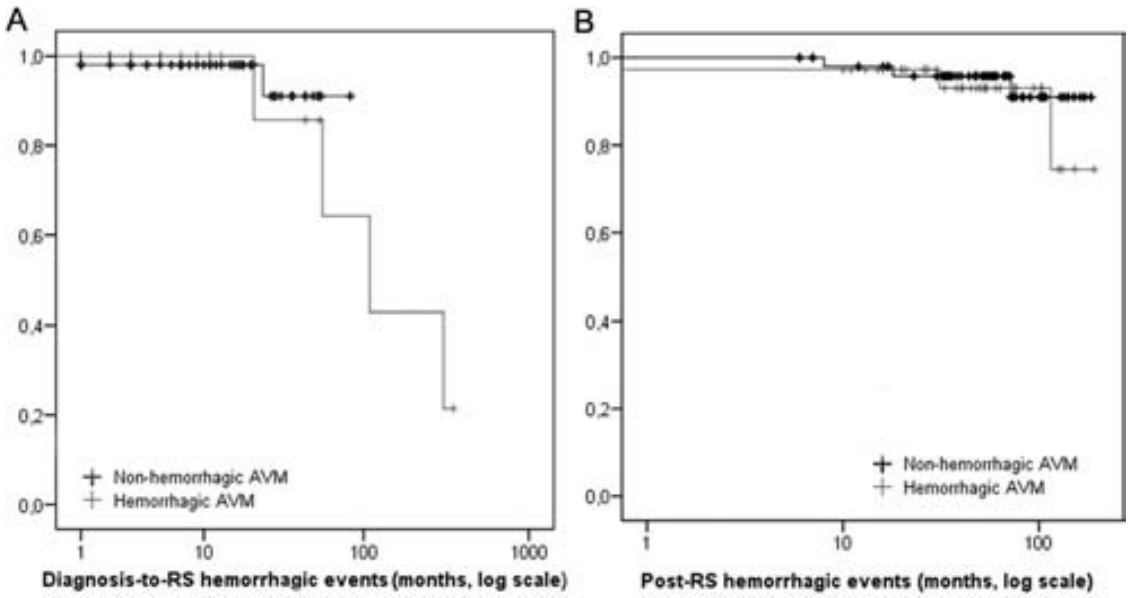

Figure 2. Kaplan-Meier survival curves for hemorrhages during the diagnosis-to-radiosurgery period (2A) and postradiosurgery period (2B).

Table 3. Evolution of Annual Hemorrhage Rates

	Hemorrhagic AVM	Non-Hemorrhagic AVM	Global
Birth-to-diagnosis	3.30%	N/A	1.20%
Diagnosis-to-radiosurgery	3.80%	2.60%	3.10%
Post-radiosurgery (first 3 y)	2.10%	1.40%	1.70%
Post-radiosurgery (3 y onward)	1.10%	0.30%	0.50%

AVM indicates arteriovenous malformations.

quently treated with embolization before undergoing radiosurgery. This treatment may carry its own risk of periprocedural hemorrhage, and also of delayed hemorrhage because of continued blood inflow into a nidus with impaired outflow.[14,15] In our series, 2.6% of nonhemorragic AVMs bled in the time between diagnosis and RS. Embolization had a hazard ratio of 2.793 for postradiosurgical bleeding rates; however, this number was not significant.

Another potential bias is a selection bias, particularly for voluminous, deep, untreatable AVMs, where obliteration is hardly the expected outcome no matter the initial combination of treatments used. In these cases, the use of radiosurgery might be spurred on by rebleeding and result in falsely higher pretreatment bleeding rates. Figure 1A illustrates this fact, highlighting that most of the radiosurgeries performed late in follow-up happened after the patient had rebleeding. Therefore, numbers pertaining to preradiosurgical bleeding risk must be interpreted with caution, both in our study and in the others.

Examining the natural history of nonhemorrhagic AVM is an alternate way to gauge the usefulness of radiosurgery. Historical and recent studies all provide very similar results, with bleeding rates of 2% to 4.2%,[16–20] and more recently of 1.3%.[21] Those rates are very similar to the ones obtained during the latency period both by Yen et al (2.2%) and in our study (2.6%). Extending the follow-up beyond the latency period reveals an important additional reduction to 0% to 0.3%. Therefore, if we use natural history for comparison, we can again conclude that radiosurgery does indeed lower the bleeding risk of both ruptured and unruptured AVM.

Obliterated AVM: No Risk or Still at Risk?

In their recent article, Yen et al reported no bleeds whatsoever after nidus obliteration, but the length of postobliteration follow-up is not clear. Other studies usually report some residual risk of hemorrhage. For example, Shin at al have found a 0.3% annual hemorrhage risk for obliterated AVMs, and 2.2% cumulative risk over 10 years (4 patients from a series of 236 angiographically confirmed cases).[22] In our series, the annual hemorrhage rate after obliteration was 0.6%. Interestingly, nidus closure was not a statistically significant protective factor in multivariate analysis. This may be because only angiographically confirmed cases were considered positive for this analysis, leaving the patients who did not want to undergo invasive procedures as false-negatives.

There can be several causes for persistence of the bleeding risk in nidi that have been exhaustively studied and confirmed closed. First, compared with the finality offered by complete microsurgical resection, the closure of a nidus via slow endothelial proliferation may prove not to be as definitive, as there are instances of repermeabilization years after complete occlusion.[23]

Table 4. Univariate and Multivariate Cox Regression Models for Postradiosurgical Hemorrhage

	Univariate Cox Regression			Multivariate Cox Regression		
	Hazard Ratio	CI Interval	*P* Value	Hazard Ratio	CI Interval	*P* Value
Age at diagnosis (decades)	1.006	0.737–1.372	0.971			
Men/women	1.135	0.423–3.049	0.801			
Previous medical history						
Smoking	2.849	1.058–7.692	0.038*	2.475	0.733–8.333	0.152
Hypertension	4.651	1.473–14.706	0.009*	4.545	2.515–16.403	0.024*
Hemorrhagic presentation	1.424	0.529–3.831	0.485			
Spetzler-Martin items						
Size <3 cm	0.221	0.077–0.633	0.005*	0.241	0.069–0.843	0.026*
Eloquent area	2.257	0.814–6.250	0.118			
Deep drainage	0.978	0.333–2.865	0.967			
Spetzler-Martin scale >2	3.021	1.127–8.065	0.028*	1.151	0.363–3.679	0.802
Cortico-subcortical AVM	1.250	0.401–3.891	0.700			
Embolization	2.793	0.794–9.804	0.109			
AVM volume (cm^3)	1.050	1.014–1.087	0.006*	1.039	0.986–1.098	0.17
Second radiosurgery	0.796	0.252–2.506	0.697			
Nidus obliteration	0.496	0.185–1.328	0.163			
Aneurysms	4.032	1.055–15.385	0.042*	5.076	1.193–21.739	0.028*
Exclusively deep drainage	1.241	0.304–5.076	0.764			
Single draining vein	0.864	0.278–2.684	0.800			

AVM indicates arteriovenous malformations.
*$P<0.05$.

Second, some AVM with negative arteriographies can still have evidence of nidus persistence on histological examination.[24–26] Last, brain-blood barrier disruption, edema, and cyst formation have been described in postradiosurgical MR studies. They are presumably unrelated to the presence of anomalous flow inside the nidus, and represent radiation-induced changes of the adjoining brain tissue. These imaging changes have been positively associated with hemorrhage.[22]

Risk Factors for Postradiosurgical Hemorrhage: Medical History Also Counts

As far as AVM characteristics go, several items such as age, deep location, smaller size, and deep drainage have been consistently identified as risk factors for hemorrhagic presentation.[13,22] The first 2 were also true in our study. Interestingly, many of those factors tend to lose relevance during the postradiosurgical period. In our case, size <3 cm and presence of aneurisms were the only significant postradiosurgical AVM-related factors after multivariate analysis.

Patient-related items other than age and sex are often not entered in hazard models for AVM bleeding. We have identified only 1 study that sought to correlate cardiovascular risk factors with initial hemorrhage, finding a positive association with hypertension.[27] We reviewed the medical history of all our patients, retrieving data on cardiovascular risk factors, and focused on smoking and arterial hypertension as potential risk factors based on data available for brain aneurysms. Both proved relevant in univariate analysis, though only hypertension was shown to be an independent factor for hemorrhage after therapy, with hazard ratio of 4.5. Beside the fact that this finding is both unconfirmed and unsurprising, it does prove that selected details of patients' medical history should be stressed in future studies.

Conclusions

Our series provide additional evidence that RS offers protection against cerebral hemorrhage caused by AVM rupture, regardless of the manner of its initial presentation. Successful obliteration, small nidus size, and absence of arterial hypertension reduce the risk of postsurgical bleeding.

Disclosures

None.

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DIAGNOSTIC NEURORADIOLOGY

Late clinical and radiological complications of stereotactical radiosurgery of arteriovenous malformations of the brain

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Abstract
Introduction Post-radiation injury of patients with brain arteriovenous malformations (AVM) include blood–brain barrier breakdown (BBBB), edema, and necrosis. Prevalence, clinical relevance, and response to treatment are poorly known. We present a series of consecutive brain AVM treated with stereotactic radiosurgery describing the appearance of radiation injury and clinical complications.
Methods Consecutive patients with annual clinical and radiological follow-up (median length 63 months). Edema and BBBB were classified in four groups (minimal, perilesional, moderate, or severe), and noted together with necrosis. Clinical symptoms of interest were intracranial hypertension, new neurological deficits, new seizures, and brain hemorrhages.
Results One hundred two cases, median age 34 years, 52 % male. Median irradiated volume 3.8 cc, dose to the margin of the nidus 18.5 Gy. Nineteen patients underwent a second radiosurgery. Only 42.2 % patients remained free from radiation injury. Edema was found in 43.1 %, blood–brain barrier breakdown in 20.6 %, necrosis in 6.9 %. Major injury (moderate or severe edema, moderate or severe BBBB, or necrosis) was found in 20 of 102 patients (19.6 %). AVM diameter >3 cm and second radiosurgery were independent predictors. Time to the worst imaging was 60 months. Patients with major radiation injury had a hazard ratio for appearance of focal deficits of 7.042 (p=0.04), of intracranial hypertension 2.857 (p=0.025), hemorrhage into occluded nidus 9.009 (p=0.079), appearance of new seizures not significant.
Conclusions Major radiation injury is frequent and increases the risk of neurological complications. Its late appearance implies that current follow-up protocols need to be extended in time.

Keywords Brain arteriovenous malformation · Stereotactical radiosurgery · Adverse radiation effects · Radionecrosis

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Introduction

Stereotactic radiosurgery (SRS) has been a viable, non-invasive option for treatment of brain arteriovenous malformations (AVMs) for more than 30 years. SRS obliterates AVMs by causing endothelial proliferation of irradiated vessels [1], but changes occur no sooner than 6 months after the procedure and typically take 2–3 years to finalize [2]. This proliferation is random, which means that it can occlude the outflow veins before occluding the nidus itself and also affect normal vessels, since doses as low as 5–9 Gy may be enough to cause changes [3].

Radiological complications of SRS are mainly related to irradiation volume and dose [4]. Magnetic resonance (MR) changes are consistent with blood–brain barrier breakdown (BBBB), edema and necrosis. Some findings are asymptomatic, others lead to clinical worsening of affected patients. Due to long-term appearance of complications, their exact prevalence, clinical relevance, and response to treatment are difficult to assess.

The goal of this study was to analyze the occurrence and clinical correlation of radiological complications of a series of consecutive patients monitored at our institution after SRS.

Methods

This study is based on a historical series of brain AVM patients treated with radiosurgery and monitored at our hospital between 1994 and 2010, as published previously [5]. Typically, patients received SRS after their AVMs were deemed unsuitable for neurosurgery (deep location, eloquent area) or further endovascular treatment (caliber of feeding arteries too small for selective catheterization). Patients with less than 1 year of follow-up were excluded. The study was approved by our hospital's Ethics Committee.

Out of 108 initial cases, 102 were monitored for at least 1 year (55 % were monitored for 5 years or more), and had complete MR and clinical records. Their median age at the time of diagnosis was 34 years (interquartile range, IQR, 22–50), and 52 % were male. There were 12 children under 18 years. Forty one patients (40 %) had been diagnosed because of brain hemorrhage, 35 % because of seizures, 14 % had headaches and 2 % focal deficits. The distribution of the Spetzler–Martin scale was as follows: grade 1 in 34 % of cases, grade 2 in 33 %, grade 3 in 25 %, and grade 4 in 8 % of cases. Nidus diameter was less than 3 cm in 74 % of patients, with a median volume of 3.95 cc (IQR 0.95–5.9). AVM were located superficially (either cortically or subcortically) in 75 % of cases. Venous drainage was superficial in 59 %, deep in 20 %, and combined in 21 %. Aneurisms were found in 14 % of cases.

Radiosurgeries

Stereotactic radiosurgery procedures were performed in single sessions with the use of Gamma Knife. A Leksell stereotaxic frame was affixed to the patient's head (Elektra AB, Stockholm, Sweden). Virtual simulations and planifications were completed with the help of MRI and digital angiography. We used a standard protocol that called for the dose of 18 Gy to be applied to the 80 % isodose line encompassing the margin of the nidus (except in nine patients treated before 2001, where the prescription was planned to the 50 % isodose). Only three patients received less than 16 Gy to the margin, for lesions located in thalamus, deep cerebellum, and brainstem. Mean dose to the margin was 18.5±4.6 Gy, range 12–24. Mean maximum dose was 24± 4.1 Gy, range 13–40. Irradiated volume ranged from 0.5 to 17.4 cc, with the median volume of 3.8 cc (IQR 2–4.6).

In 66 cases (64.7 %), endovascular embolizations were performed a mean of 8±12 months before SRS to reduce the size of the nidus. *n*-BCA (*n*-butylocyanoacrylate) mixed with Lipiodol was used until 2007 and EVOH (ethylene vinyl alcohol) copolymer dissolved in DMSO (dimethyl sulfoxide) after 2007. Median number of embolization sessions was 2.5 (range 1–4). Two patients underwent a microsurgical procedure before SRS that failed to remove the AVM, and one patient received both endovascular and surgical treatment.

Clinical follow-up

Clinical data were obtained through the review of neurological, neurosurgical, and neuroradiological records (typically, asymptomatic patients were monitored biannually during the first year and annually afterwards), as well as documents pertaining visits to the emergency department. Diagnoses of interest were: intracranial hypertension (complaints of headaches, nausea, vomiting together with compatible neurological examination and ophthalmoscopy), development of new neurological deficits or clearly documented worsening of pre-existent ones, brain hemorrhage (development of new symptoms together with radiological signs of acute bleeding on cerebral tomography (CT) or MR) and appearance of new seizures. All subsequent treatments and clinical response to them were also recorded.

Radiological data

Patients' annual radiological follow-up consisted of serialized contrast-enhanced MR in GE or Siemens 1.5 T scanner, sagittal sequences FSE T1 weighted, axial PD/T2-weighted, coronal FLAIR, Echo Planar Imaging Diffusion (b=1000), Gradient Echo, and FSE T1-weighted with gadolinium. If the patient complained of new or worsening neurological symptoms, an urgent CT scan followed by scheduled MR was performed. Radiological follow-up continued even after nidus occlusion was confirmed. The definition of nidus obliteration was based on angiographic criteria in all cases: absence of abnormal vessels in the area of the nidus, normalization of the draining veins and normal circulation time [6]. If the malformation was still clearly patent on MR or angiography after 4 years, the possibility of a second radiosurgery was explored.

All available data were reviewed by a team of two neuroradiologists blinded to the symptoms of the patients. Initial AVM characteristics (nidus size, volume, location, drainage and presence of intranidal aneurisms) as seen on pre-SRS digital angiography and initial MR were recorded according to published standards [7]. In order to grade the radiation effects, a previously published rating system was used [4]. Vasogenic edema was defined as hyperintensity on T2 and FLAIR sequences and quantified as no reaction, minimal (traces or incomplete rim), perilesional (a narrow rim with high signal intensities surrounding the nidus), moderate (a lesion with high signal intensities surrounding the AVM and

occupying less than one-fourth of the brain), and severe reaction (a lesion occupying more than one-fourth of the brain). The assessment of BBBB was performed through the detection of hyperintense signals on contrast-enhanced T1-weighted images compared to non-enhanced images, and also classified as minimal, perilesional, moderate, and severe according to the same criteria (Fig 1). Finally, necrosis was defined by the presence of a T1 hypointensity and a circular contrast enhancement. It also included cyst formations.

Finally, for the purpose of statistical analysis, we defined a combined variable called "major radiological injury" that included moderate or severe edema, moderate or severe BBBB, or necrosis.

Statistical treatment

Data are reported as mean ± standard deviation, or median and IQR.

Univariate and multivariate logistic regression is used for analysis of appearance of radiation injury and subsequent clinical manifestations. The following variables are examined: demographic (sex, age), clinical (hemorrhagic versus non-hemorrhagic AVM, previous embolization, nidus closure), radiological (AVM location, drainage, diameter), and radiosurgical (irradiated volume, marginal dose, maximum dose, repeated SRS). Hazard ratios with 95 % confidence intervals are presented.

Kaplan–Meier survival curves and log rank are used to represent the appearance of radiological injury over time.

$P<0.05$ is considered to be statistically significant.

Results

Radiological follow-up

Median length of follow-up was 63 months since the date of SRS (35–103). Eighty three patients (81.4 %) had a single SRS. Of these, 20 had not yet undergone the digital angiography (less than 3 years of follow-up after SRS or rejection of the procedure), the rest had a nidus closure rate of 79 %. Nineteen patients (18.6 %) underwent a second SRS, some 44 months after the first one, and were monitored for additional 54 months (36–103) after this second procedure. Eleven (57.9 %) had angiographical confirmation of nidus closure, 4 showed persistence of flow on angiography and 4 persistence of AVM on MRI.

Only 43 patients (42.2 %) remained free from any radiological injury during the entirety of the follow-up. Vasogenic edema of any intensity was found in 44 patients (43.1 %) at some point. Blood–brain barrier breakdown of any intensity was observed in 21 patients (20.6 %). Necrosis was found in seven patients (6.9 %). The exact frequencies are represented in Table 1.

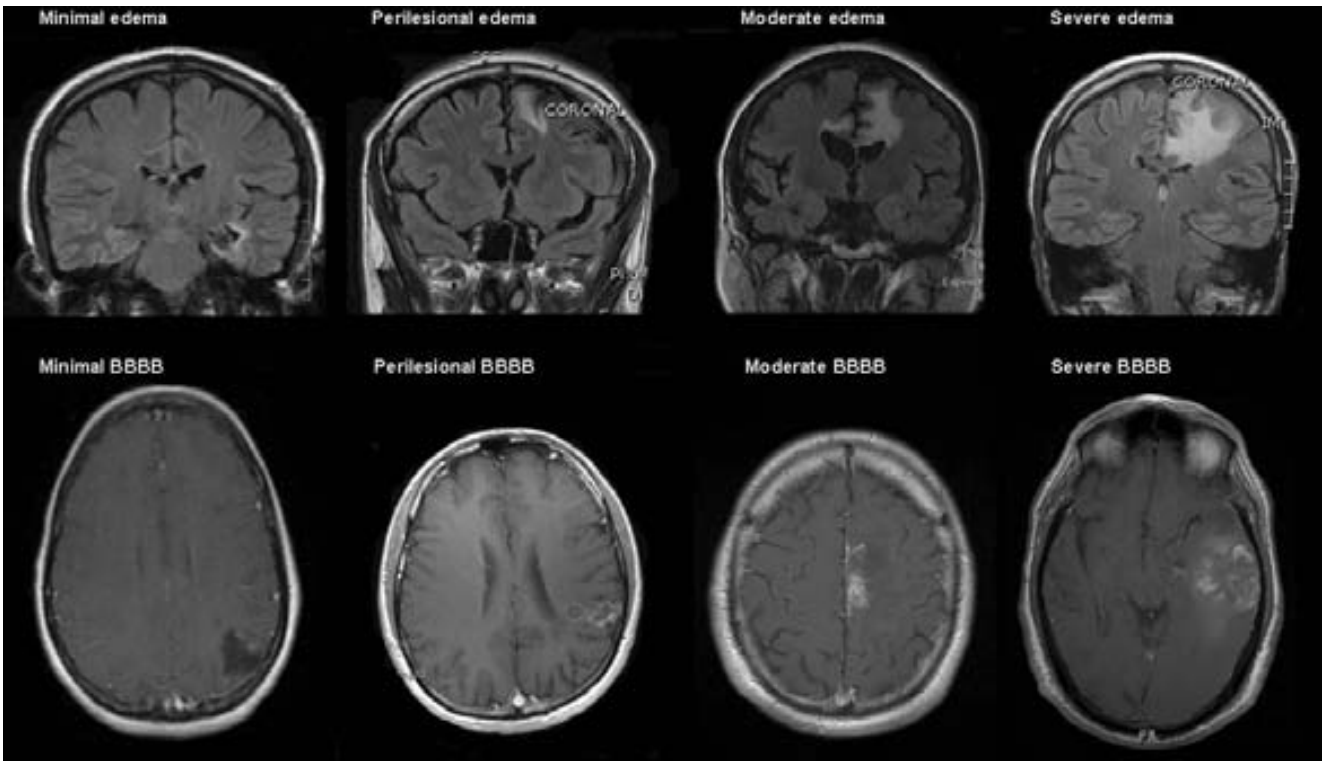

Fig. 1 Radiological classification used in this article

Table 1 Percentages of different types of radiological injury

	Edema	BBBB	Necrosis
Minimal	20 (19.6 %)	9 (8.8 %)	
Perilesional	7 (6.9 %)	8 (7.8 %)	
Less than ¼	9 (8.8 %)	2 (2 %)	
More than ¼	8 (7.8 %)	2 (2 %)	
Total:	44 (43.1 %)	21 (20.6 %)	7 (6.9 %)

The combined variable of major radiological injury, as defined earlier, was found in 20 of the 102 patients (19.6 %). Overall, edema was the item that contributed most frequently (85 %), followed by necrosis (35 %), and BBBB (20 %). The median time to the worst findings on any of patient's MRI was 60 months (IQR 32–101).

Table 2 shows the results of univariate analysis. The appearance of major radiological injury was unrelated to the clinical presentation of AVM (hemorrhagic versus non-hemorrhagic), location, type of drainage, embolization prior to SRS or nidus closure. It did significantly correlate with irradiated volume (hazard ratio 1.288, $p=0.043$), AVM diameter >3 cm (HR 4.062, $p=0.007$), and second SRS (HR 5.917, $p=0.001$). The lowest significant cut point for nidus volume was 5 cm^3. When the above parameters were entered into a multivariate model, only diameter >3 cm and second radiosurgery remained as independent predictors of major radiological injury (see Fig 2 for Kaplan–Meier survival curves).

Clinical follow-up

Nineteen patients (18.6 %) presented with new neurological complaints, though some of the symptoms had well-defined causes and were not attributable to SRS (see below).

Non-hemorrhagic focal deficit, 5.8 % Six patients developed new focal deficits during follow-up. One patient's problem was directly related to a microsurgery performed 52 months after the SRS (this patient was excluded from the hazard ratio analysis.). There were three instances of early focal deficit occurring during the first 6 months post-SRS, one of them associated with necrosis. The last two instances were detected at 90 and 130 months, and were associated with major edema.

Intracranial hypertension, 3.9 % Four patients had suggestive symptoms and clinical evaluation, a median of 42 months (IQR 17–130) after treatment. Three of them presented with major edema, BBBB, and in one instance necrosis. One case had thrombosis of the main draining vein and only minimal edema on MRI.

New seizures, 1.9 % There were two patients with new seizures, one with a single partial seizure 34 months after SRS and another one who suffered 1–2 annual partial seizures with secondary generalization since 3 months after SRS. Their appearance was not connected to any form of radiological injury.

Brain hemorrhage, 6.8 % Overall, there were seven instances of intracerebral bleeding after SRS. Four cases had a patent nidus and were excluded from further analysis, since it was assumed that the hemorrhage was a consequence of persistent AVM and not a complication of SRS. The three instances of hemorrhage into angiographically confirmed occluded nidus (2.9 %) happened 72, 99 and 160 months after SRS. Two cases had major edema and BBBB at the time of bleeding, and one had grade 2 edema.

Death Occurred in four patients (3.9 %), two of cerebral hemorrhage (one case with permeable nidus and one case with closed nidus and necrosis), and two of unrelated causes (lung and liver cancer).

Correlation between radiological findings and clinical complications

Overall, 7 of the 20 cases with major radiological injury had clinical complications (35 %) as opposed to 6 of the 62 patients without (9.6 %). Such patients had high hazard ratios for developing intracranial hypertension, neurological deficits and hemorrhage, but not seizures (HR for each individual complication are presented in Table 3). Moderate or severe edema, moderate or severe BBBB, and necrosis were all independently related to clinical complications. The existence of minimal or perilesional edema or BBBB was not connected with symptoms.

Response to treatment

Asymptomatic, untreated major radiological injury (13 cases) Eight patients remained radiologically stable. Four slowly progressed (two growing cysts between years 5–11 and 13–16, and two increasing edemas between years 1–3 and 2–6). One patient presented spontaneous improvement, with regression of edema 5 years after SRS (Fig 3).

Symptomatic, untreated major radiological injury (two cases) One patient remained stable and one suffered a gradual worsening of his symptoms, eventually leading to intracerebral hemorrhage and surgical resection of the necrotic lesion.

Symptomatic, treated major radiological injury (five cases) All received corticosteroids, either remaining stable (two patients) or clinically improving (three patients). One

Table 2 Univariate and multivariate regression analysis for incidence of radiation injury

	Univariate analysis		Multivariate analysis	
	Hazard ratio	*p*	Hazard ratio	*p*
Sex	1.950	0.196		
Age (decades)	1.091	0.533		
Hemorrhagic AVM	0.760	0.598		
Superficial[a] location	0.704	0.526		
Excl. deep drainage	0.201	0.131		
Prior embolization	1.346	0.581		
Nidus closure	1.315	0.598		
Irradiated volume	1.288	0.043**	0.993	0.913
Diameter >3 cm	4.062	0.007**	14.452	0.004**
Volume <5 cm^3	3.588	0.033**	0.872	0.894
Second SRS	5.917	0.001**	14.286	0.002**
Dose to margin	0.905	0.628		
Maximum dose >25	2.707	0.082		

[a]Cortical or subcortical

**$p<0.05$

female patient with extensive necrosis was additionally treated with hyperbaric oxygen, showing some improvement in the frequency of the epileptic seizures she had suffered since before SRS, but no clear radiological improvement

Discussion

The consequences of brain irradiation are difficult to evaluate due to their variability and lack of consensus on how to best grade and describe radiological findings. Literature offers little concordance on this topic, describing post-SRS lesions as "radionecrosis", "post radiation injury", "adverse radiation effects", "delayed radionecrotic masses", and so on. Thus, the frequency with which said findings are reported varies from one study to another. Numbers go from 2.2–9 % for necrotic masses according to Foroughi et al. [8], to 60 % for radiation-induced edema according to Ganz et al. [9]. Radiation dose and target volume are the most common predictors for radiological injury [9–11]. Prior hemorrhage [10], AVM location [12], and repeated radiosurgery [13] have been described in some series, but not in others. For our part, multivariate analysis found a correlation of radiological injury with AVM diameter >3 cm and second SRS.

Beside radiological definition, length of follow-up is also a crucial factor, since radiological injuries are accumulative and, in our experience, remissions of late and severe cases are rare. In our series, median time to the worst findings on serialized MRIs was 60 months (IQR 32–101), a number that is very close to the total length of follow-up (63 months). This probably shows that the more time we monitor our patients, the more severe radiological injury we are likely to encounter.

Overall, MR findings that have been attributed to SRS include cysts and necrotic masses [8], edema, blood–brain

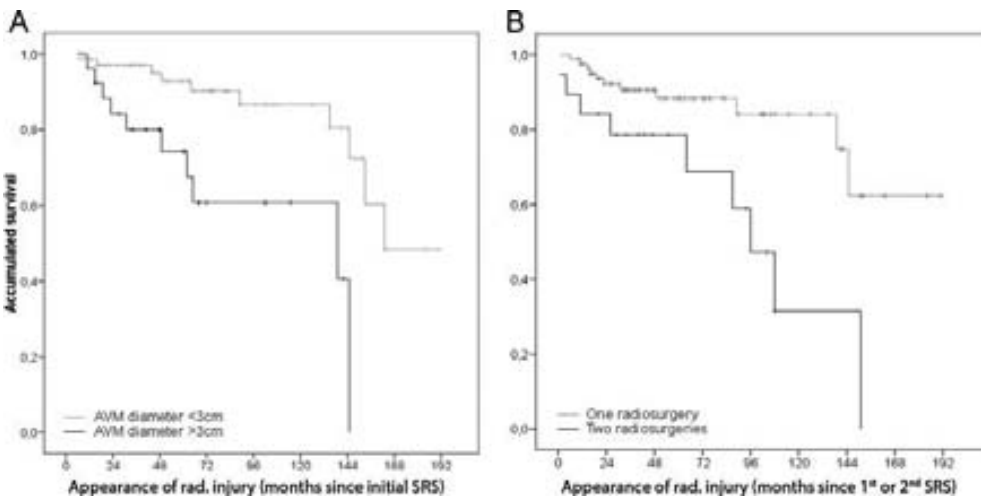

Fig. 2 Kaplan–Meier survival curves for the appearance of radiological injury in patients with AVM diameter < and >3 cm (**a**, log rank=0.001), and with one or two radiosurgeries (**b**, log rank=0.002)

Table 3 Hazard ratios for appearance of different clinical complications in patients with major radiological injury

	Hazard ratio	HR confidence interval	*p*
Focal deficit	7.042	1.094–45.455	0.04
Intracranial HT[a]	2.857	1.401–42.857	0.025
Seizure			NS
Hemorrhage into occluded nidus	9.009	0.773–10.000	0.079

[a] Intracranial hypertension

barrier breakdown [4], and intracranial vessel stenosis [14, 15]. All of the above except stenosis can be easily evaluated on contrast-enhanced MR, which is the standard imaging technique for irradiated AVMs. The exact pathogenesis of each complication is unknown, same as their prognostic value. For instance, some authors have suggested that early edema could be a manifestation of quick closure of the AVM [16]. Radiation-induced BBBB poses a different diagnostic challenge, since it must be differentiated from contrast uptake into a permeable nidus. Necrosis is an altogether different entity both in prognosis (highly unlikely to remit) and treatment (some cases can be treated with surgery) [8].

As important as the type of radiological injury is, the extension of the lesion will probably be more relevant to the appearance of clinical symptoms. To date, there is no consensus on the best way to grade the lesion size. Some authors calculate the individual volumes of T2 signal changes [10]. Several simpler scales have also been reported [17]. We have used the one proposed by Levergrün et al. [4] due to its easy applicability and systematical assessment of each type of radiological injury (edema, BBBB, and necrosis). This approach allowed us to differentiate between small, frequently found areas of edema that were unlikely to cause symptoms, and sized lesions that could be truly problematic. We found minimal or perilesional edema in almost 25 % of patients, and minimal or perilesional BBBB in 16 % (their existence was not related to appearance of clinical complications). Overall, more than a half of our cases had some kind of radiological injury, but only 19.6 % had lesions sizable enough to be labeled as major.

Regarding clinical manifestations, a similar problem of definitions arises. Studies that report clinical complications of SRS sometimes include the appearance of cysts and necrosis (silent radiological findings) into their rates. Another controversial procedure is to count brain hemorrhage among late complications, while failing to take into account whether the AVM was permeable at the time of bleeding. Since many AVMs debut with hemorrhages that are likely to leave preexistent deficits, appearance or progression of focal symptoms must always be evaluated by experienced neurologists [18]. Finally, intracranial hypertension is difficult to define.

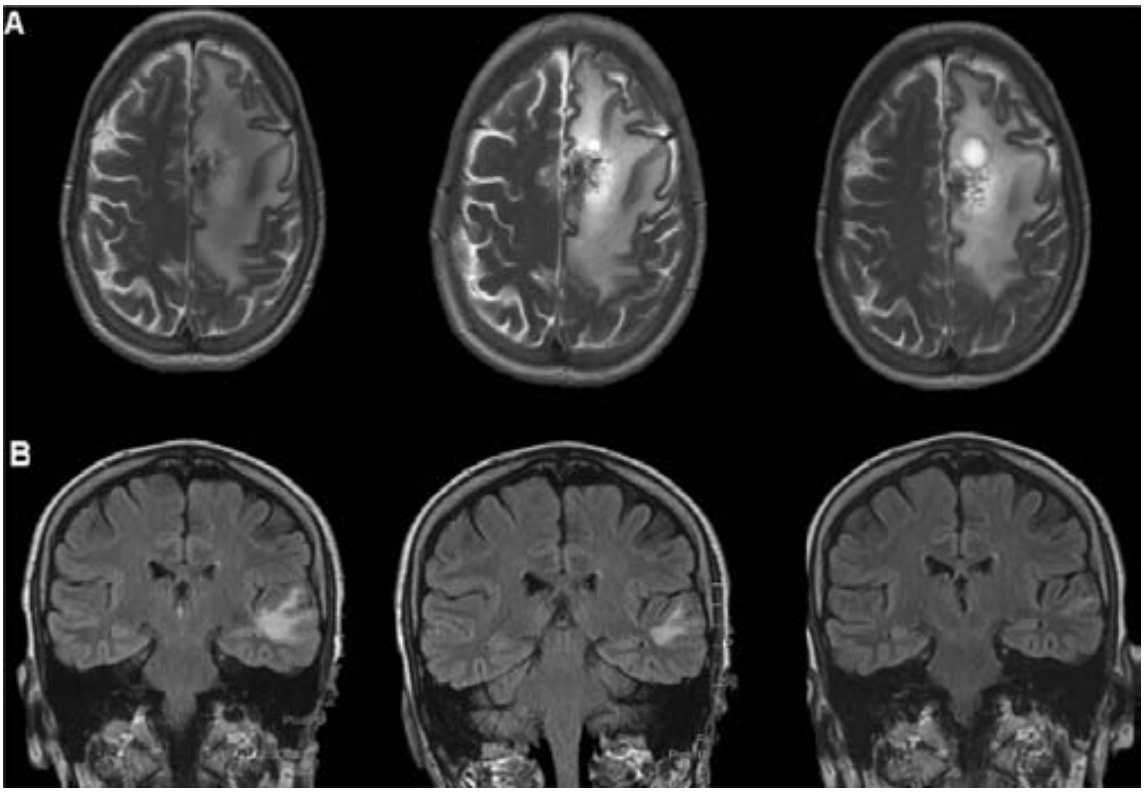

Fig. 3 Evolution of radiological injury in time (yearly studies). **a** Growing edema and cyst formation. **b** Fading of edema in an untreated patient

Headache is a common pre-existing complaint among non-hemorrhagic AVM patients, since it is frequently the reason behind the imaging study responsible for the diagnosis. Again, neurological expertise and careful search for signs of papilledema are needed to differentiate casual headaches from intracranial hypertension due to SRS.

Existent literature puts clinical morbidity from neurological deficits at a level as low as 6.3 % [19] or as high as 19.2 % [11], with most studies reporting numbers in between (hemiparesis 8.3 % [9] or assorted focal deficits 9.4 % [14]). In studies that consider all kinds of symptoms (headaches, new seizures, and new focal neurological deficits), the rates range from 9 to 27 % [10, 12]. The highest morbidity was reported at 34 % (17 out of 50 patients), though in this study it was not clear whether all symptoms (for example cognitive deficits) were directly related to SRS [20].

Our study reported an overall clinical complication rate of 18.6 %, and 13.7 % after excluding deficits derived from post-SRS surgical interventions and hemorrhages into permeable nidus. The presence of major radiological injury increased the hazard ratio for focal deficits and intracranial hypertension, but not for seizures. There was also an association with brain hemorrhage after nidus closure (bleeding after obliteration is rare but not impossible, and has been reported in connection with contrast enhancement of the nidus on CT or MR [21, 22]). There was no correlation between type of radiological injury (edema, BBBB, or necrosis) and type of clinical complication.

The impact of any therapy on the prognosis of either radiological findings or clinical symptoms is difficult to assess, as natural history of such complications remains scarcely studied. Among our untreated cases, one patient presented a complete regression of edema within 2 years of its development; though eight further cases remained stable and four cases progressed, suggesting that spontaneous remission is possible, but overall unlikely.

Treatment with corticosteroids seemed to generate a modest benefit [23], as three out of five patients improved while two remained stable. Treatment with hyperbaric oxygen therapy was attempted in one patient with voluminous necrosis, but contrary to other reports [24] did not yield positive radiological results. Surgical removal was undertaken in one case after a bleeding occurred, removing both the hematoma and the necrotic lesion [25].

Conclusions

Major radiation effects can be found in almost 20 % of cases after SRS, increasing the risk of delayed neurological deficit sevenfold, the risk of intracranial hypertension almost threefold, and probably contributing to hemorrhaging of already closed AVMs. Their late appearance supports the notion that our current follow-up protocols need to be reviewed and extended in time. The introduction of a standardized scoring system that would grade the type of radiological injury, their size and clinical relevance would be the first step toward improving our knowledge of late onset complications of SRS.

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Conflict of interest We declare that we have no conflict of interest.

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5. RESUMEN DE RESULTADOS

Un total de 108 pacientes fueron incluidos en el estudio. La edad media en el momento del diagnóstico fue de 36 años (rango 4-73 años), 55% eran hombres. El 39.8% de las MAV fueron hemorrágicas, del resto la mayoría fue diagnosticada tras crisis epilépticas (32.4%) o cefaleas (15.7%). La mayoría (78%) tenía un nido de localización córtico-subcortical, con un volumen mediano de 5.8 cm^2. Aproximadamente dos tercios de los pacientes recibieron tratamiento endovascular previo a la radiación. Un 15.7% de MAV estaban asociadas a un aneurisma. Veinte pacientes (18.5%) recibieron una segunda radiocirugía tras constatarse un nido aún patente pasado el período de latencia. Para el desglose exacto de los datos demográficos, las características de las malformaciones y la forma inicial de presentación véase Tabla 1 del Artículo 1.

El porcentaje de MAVs ocluidas con éxito fue de 65% (71 de los 108 casos). El seguimiento medio tras la aplicación del tratamiento fue de 65 meses.

5.1. TASAS DE HEMORRAGIA:

El análisis pormenorizado puede encontrarse en el Artículo 1, junto con las curvas de Kaplan-Meier correspondientes a cada periodo analizado (véase Figura 1 para el período pre-diagnóstico y Figura 2 para el período post-diagnóstico).

- Nacimiento hasta diagnóstico: asumiendo que una persona se encuentra en peligro de sangrado desde el nacimiento, el tiempo colectivo en riesgo ascendió a 3909 años, durante los cuales se detectaron 46 eventos. Esto arroja una tasa global anual de hemorragia de 1.2%, y una tasa específica para las MAV hemorrágicas de 3.3%.

- Período desde el diagnóstico hasta la RC: el tiempo medio desde el diagnóstico al tratamiento fue de 25 meses. El retraso se explica porque la mayoría de pacientes recibieron embolizaciones (típicamente múltiples, con una mediana de 3 sesiones) con el fin de disminuir el tamaño del nido y mejorar sus expectativas antes de someterse a RC. En este período se detectaron 7 sangrados más, siendo la tasa de 2.6% en MAV no hemorrágicas, y de 3.8% en MAV hemorrágicas.
- Los 3 primeros años tras la RC la cohorte hemorrágica tuvo una tasa de resangrado anual de 2.1% (2 casos en 1113 meses cumulativos en riesgo), y la no hemorrágica de 1.4% (2 casos en 3582 meses).
- Pasados los 3 años tras la RC, las cifras disminuyeron a 1.1% anual para las MAV hemorrágicas y 0.3% para las no-hemorrágicas, respectivamente.
- El resumen de estas cifras está recogido en la Tabla 3 del Artículo 1.

Si analizamos por separado a los pacientes en los que se logró la oclusión completa del nido de la MAV (71 casos), comprobamos que tras confirmarse ese extremo ofrecieron la tasa de sangrado muy baja, de solo 0,6% anual.

En cuanto a los factores predictivos de un sangrado, se realizaron comprobaciones en dos períodos diferentes: antes y después de la radiocirugía. Factores relacionados con las MAV (tamaño, gradación de Spetzler-Martin, localización, presencia de aneurismas, tipo de drenaje), con la historia personal (edad, hábito tabáquico e hipertensión) y con el tratamiento (embolizaciones previas, oclusión del nido) fueron analizados mediante un modelo univariante, y las variables significativas se incluyeron en un análisis multivariante.

Para el período pre-tratamiento, se mostraron como factores de riesgo la edad más joven, la localización diferente de la córtico-subcortical y una vena de drenaje única (Tabla 2, Artículo 1).

En el período post-tratamiento, en el análisis multivariante se mostraron como factores independientes de mal pronóstico asociados a hemorragia la hipertensión, el diámetro inicial del nido mayor de 3 cm. y la presencia de aneurismas (Tabla 4, Artículo 1).

5.2. COMPLICACIONES TARDÍAS:

5.2.1. Complicaciones radiológicas:

Solo un 42% de pacientes no presentó ningún tipo de alteración nueva en las pruebas de imagen durante la duración del seguimiento. La aparición del edema vasogénico fue observado en el 43%, si bien la mayoría de las lesiones fue clasificada como mínima o perilesional. Solo en 16% de los casos se encontró un edema moderado (ocupante de menos de ¼ de la superficie del corte) o grave (más de ¼). De manera similar, la rotura de la barrera hematoencefálica fue anotada en 20.6% de casos, pero solo fue moderada o grave en 4%. Un 7% de pacientes mostró necrosis franca. El desglose de estas cifras puede encontrarse en la Tabla 1 del Artículo 2.

Ya que muchos de los hallazgos estaban solapados en un mismo paciente (por ejemplo, edema y necrosis), se creó la variable combinada de “lesión radiológica mayor”, definida como necrosis, edema y/o rotura de la BHE con exclusión de todas las lesiones mínimas o perilesionales. Esta variable fue positiva en 20% de los pacientes. Los factores que se asociaron de forma independiente con la aparición de las lesiones radiológicas mayores fueron el diámetro del nido de la malformación mayor de 3 cm y el tratamiento con dos radiocirugías (véanse Tabla 2 y Figura 2 del Artículo 2).

Para evaluar el momento temporal en que aparecieron las lesiones se han realizado las correspondientes curvas de Kaplan-Meier, que pueden encontrarse en la Figura 2 del Artículo 2. Como puede observarse, se han estado detectando lesiones durante todas las fases del seguimiento. Como los hallazgos podían cambiar en el tiempo (progresar o remitir espontáneamente), se escogió entre las resonancias anuales aquella con los hallazgos más graves y se anotó la fecha de su realización. El tiempo mediano desde la RC hasta el peor hallazgo en imagen fue de 60 meses.

Los factores de mal pronóstico que se asociaron a la aparición de lesiones radiológicas fueron el diámetro del nido mayor de 3 cm. y aplicación de una segunda radiocirugía (véase Tabla 2 Artículo 2).

En cuanto a la evolución en el tiempo, detectamos un total de 13 lesiones radiológicas mayores que permanecieron clínicamente asintomáticas (las lesiones sintomáticas se discuten más adelante). Ninguna recibió un tratamiento médico especial. Ocho lesiones permanecieron estables en el tiempo, cuatro mostraron una lenta progresión (dos mostraron formación de quistes, y dos un lento crecimiento del edema). Sin embargo, un paciente presentó una regresión espontánea del edema unos 5 años tras recibir su RC. Para ejemplos gráficos de progresión y remisión véase Figura 3 del Artículo 2

5.2.2. Complicaciones clínicas:

- Déficit focal no asociado a hemorragia: 5.8% (6 casos, aunque uno de ellos estuvo directamente asociado con una microcirugía cerebral).
- Hipertensión endocraneal: 3.9% (4 casos). Tres de ellos desarrollaron importantes edemas, y el cuarto presentó una trombosis venosa.
- Crisis epilépticas de nueva aparición: 1.9% (2 casos). Ninguno presentó importantes lesiones en RM.
- Hemorragias intracerebrales: 6.8% (7 casos). Cuatro tenían una MAV aún permeable, que presumiblemente causó el sangrado. De los 3 casos con nido cerrado confirmado angiográficamente, 2 tenían importante edema y rotura de BHE y el último presentaba edema perilesional. Los tiempos desde el tratamiento hasta el sangrado fueron de 72, 99 y 160 meses.
- Muerte: 3.9% (4 casos). Dos por hemorragia cerebral y dos por neoplasias extracerebrales.

En general, 35% de pacientes con lesión radiológica mayor presentaron manifestaciones clínicas asociadas a estas lesiones, mientras que solo 9.6% de pacientes sin ella hicieron lo propio. El cálculo de riesgo para cada una de las complicaciones clínicas está recogido en la Tabla 3 del Artículo 2.

De los 7 pacientes que presentaron clínica asociada a una lesión radiológica mayor, 5 fueron tratados con glucocorticoides, permaneciendo estable 2 de ellos y mejorando 3. De los 2 pacientes que no recibieron este tratamiento, uno permaneció estable y otro empeoró, llegando más tarde a presentar una hemorragia intracerebral y recibiendo una resección quirúrgica de su lesión necrótica.

6. DISCUSIÓN:

Se sabe que la radiocirugía oblitera entre el 70 y el 90% de las MAV cerebrales [8]. La pregunta de si con ello disminuye el riesgo de hemorragia de absolutamente todos los tipos de MAV no se ha contestado todavía de una forma contundente [21]. *Maryuama et al* demostraron que el riesgo disminuye claramente tras el tratamiento para las MAV no seleccionadas y para las hemorrágicas, pero solo pudieron demostrar una tendencia positiva no significativa para las MAV no hemorrágicas [22]. En otro estudio de *Yen et al* [18], en el grupo no hemorrágico, las tasas bajaron de 3.9% a 2.2%. En el presente estudio, tanto en las MAV hemorrágicas como las no hemorrágicas, las tasas de sangrado mostraron cierto aumento en el período entre el diagnóstico y la RC, para caer en los años siguientes a niveles más bajos que los iniciales. El mejor pronóstico de las MAV no hemorrágicas con respecto a las hemorrágicas, y las MAV tratadas respecto a las no tratadas, se mantuvo en todos los períodos calculados.

El peor pronóstico en el período entre diagnóstico y el tratamiento no está confirmado por otros estudios, ya que la mayoría no diferencian este período concreto, incluyéndolo junto con el de pre-tratamiento. Sin embargo, intuitivamente se puede entender que se trata de un momento de mayor inestabilidad clínica, en el que la MAV ha dado por primera vez signos de su existencia que han llevado a su diagnóstico, y que por tanto el riesgo de sangrado o re-sangrado puede ser mayor. Un segundo factor a tener en cuenta podría ser el tratamiento coadyuvante con embolizaciones que tiene lugar en este período. En nuestro estudio las embolizaciones no se han asociado a un mayor riesgo de sangrado, pero otros informes las han señalado como potencial factor de riesgo [23,24].

Un hallazgo interesante y novedoso de nuestro estudio se debió a la inclusión de factores de riesgo clínicos que típicamente se asocian a

hemorragias intracraneales en los modelos multifactoriales de riesgo. La hipertensión fue, junto con el tamaño del nido y la presencia de aneurismas, un factor independiente predictor de hemorragia tras el tratamiento. Al tratarse de un factor modificable, ha de tenerse muy en cuenta a la hora de instaurar un tratamiento multidisciplinar y multifactorial para estos pacientes.

La obliteración del nido es, sin duda, una excelente noticia para los pacientes tratados. Una pregunta de gran relevancia que se hace con frecuencia es la del riesgo residual tras el completo cierre de la MAV. En el presente estudio, éste se valoró en un 0.6%. La razón por la que una MAV completamente cerrada, con arteriografía digital normal, pueda presentar un sangrado se desconoce, pero existen varias teorías que van desde la repermeabilización tardía [25] a disrupción de la barrera hematoencefálica como complicación de la propia radiocirugía. En nuestra serie, la aparición de importantes lesiones radiológicas se asoció con hemorragia en el lecho ocluido de la MAV, aunque esta asociación no alcanzó significación estadística.

Hablando de lesiones radiológicas, una de las grandes dificultades en su estudio y su tipificación es la falta de consenso en cuando a su definición. La forma de gradarlas y la frecuencia de su diagnóstico varían ampliamente en todos los estudios encontrados en la literatura. Los números fluctúan entre 2.2-8% en el estudio de *Foroughi et al* que sólo contó las masas necróticas [14] hasta el 60% de edema post-radiación en el trabajo de *Ganz et al* [15]. El volumen irradiado y la dosis utilizada en la RC son los factores predictivos más comúnmente descritos. En nuestro caso, efectivamente, las variables independientes fueron el volumen mayor de 3 cm y la segunda radiocirugía.

Un aspecto importante es el momento de la aparición de las lesiones. En nuestro estudio los peores hallazgos en resonancia fueron detectados a los 60 meses tras el tratamiento, lo cual está muy cerca de los 63 meses de seguimiento medio de nuestros pacientes. De ello podemos deducir que a

pesar del largo período de observación probablemente encontraríamos aún más lesiones de proseguir con el seguimiento.

Aunque las lesiones radiológicas son importantes, las consecuencias clínicas lo son más aún. La relación entre ambas no es proporcional, pero sí que observamos una Odds Ratio significativamente incrementada para la hipertensión intracraneal (2.8) y déficit focales (7.0) en pacientes con importantes lesiones en resonancia. La aparición de crisis epilépticas y hemorragias dentro del nido ocluido no fue estadísticamente significativa. Contabilizados globalmente, la aparición de nuevos problemas neurológicos se observó en un 13.7% de pacientes, lo que está en línea con otros estudios comparables que señalan cifras entre el 6.3% y el 34% [15, 26-29].

7. CONCLUSIONES FINALES:

1a) Los pacientes con MAVs tratadas con radiocirugía tienen menos hemorragias cerebrales tras la aplicación de este tratamiento. Las tasas de sangrado de las MAV hemorrágicas baja de 3.3% a 1.1%, y de las MAV no hemorrágicas a 0.3%. Ello demuestra la utilidad de la RC en la protección contra la hemorragia cerebral causada por la rotura de malformaciones arteriovenosas, independientemente de la forma inicial de la presentación de dichas MAVs.

1b) La ausencia de aneurismas, pequeño tamaño del nido y la ausencia de hipertensión arterial reducen el riesgo del sangrado post tratamiento.

2a) Importantes lesiones radiológicas acaban apareciendo pasados unos 5 años en el 20% de los pacientes tratados. El riesgo global de desarrollar nuevas complicaciones clínicas se cifra en un 13.7%. La aparición tardía de estas complicaciones sugiere que los protocolos de seguimiento de estos pacientes han de alargarse en el tiempo.

2b) Los factores contribuyentes al desarrollo de complicaciones son el diámetro del nido mayor de 3 cm. y tratamiento con dos radiocirugías.

La decisión de tratamiento mediante radiocirugía estereotáxica debe ser tomada de manera individual conjuntamente por el paciente y el equipo multidisciplinar que le atiende, sopesando el riesgo acumulativo de hemorragia a lo largo de la vida, el efecto psicológico de vivir con una MAV y los posibles efectos secundarios del tratamiento. Una investigación continua en este campo permitirá ofrecer datos más exactos y mejorar nuestra atención a los pacientes con esta grave patología.

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