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CLINICAL ARTICLE

A historical analysis of single-stage gamma knife radiosurgical treatment for large arteriovenous malformations: evolution and outcomes

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Abstract
Background Large arteriovenous malformations (AVMs) remain challenging and difficult to treat, reflected by evolving strategies developed from simple radiosurgical plans, to encompass embolization and, recently, staged volume treatments. To establish a baseline for future practice, we reviewed our clinical experience.
Method The outcomes for 492 patients (564 treatments) with AVMs >10 cm^3 treated by single-stage radiosurgery were retrospectively analysed in terms of planning, previous embolization and size.
Results Twenty-eight percent of the patients presented with haemorrhage at a median age of 29 years (range: 2–75). From 1986 to 1993 (157 patients) plans were simplistic, based on angiography using a median of 2 isocentres and a marginal dose of 23 Gy covering 45-70% of the AVM (median volume 15.7 cm^3). From 1994 to 2000 (225 patients) plans became more sophisticated, a median of 5 isocentres was used, covering 64-95% of the AVM (14.6 cm^3), with a marginal dose of 21 Gy. Since 2000, MRI has been used with angiography to plan for 182 patients. Median isocentres increased to 7 with similar coverage (62-94%) of the AVM (14.3 cm^3) and marginal dose of 21 Gy. Twenty-seven percent, 30% and 52% of patients achieved obliteration at 4 years, respectively. The proportion of prior embolization increased from 9% to 44% during the study. Excluding the embolized patients, improvement in planning increased obliteration rates from 28% to 36% and finally 63%. Improving treatment plans did not significantly decrease the rate of persisting radiation-induced side effects (12–16.5%). Complication rate rose with increasing size. One hundred and twenty-three patients underwent a second radiosurgical treatment, with a 64% obliteration rate, and mild and rare complications (6%).
Conclusions Better visualization of the nidus with multimodality imaging improved obliteration rates without changing morbidity. Our results support the view that prior embolization can make interpretation of the nidus more difficult, reducing obliteration rate. It will be important to see how results of staged volume radiosurgery compare with this historical material.

Keywords Arteriovenous malformation · Haemorrhage · Gamma knife · Radiosurgery · Embolization

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Introduction

Large arteriovenous malformations (AVMs) remain challenging and difficult to treat, and lesions larger than 3 cm in

diameter (or larger than 10 cm^3) are traditionally considered to be unattractive candidates for radiosurgical treatment [22, 29, 30]. However, these AVMs are unattractive not only for radiosurgery but also for other treatment modalities [6, 18]; therefore several strategies have been evolved to treat these lesions, including developing techniques of single [12, 22, 38] and multimodality treatments [2, 18].

Radiosurgery induces progressive hyalinization, proliferation of myofibroblasts and subsequent thrombo-obliteration, leading to complete radiological obliteration in 50–80% of the AVMs within 2–4 years, depending on size [30, 35, 44]. Being minimally invasive and a low-risk treatment, it may serve a real management alternative even for large lesions. Radiosurgical treatment of large AVMs has evolved from simple radiosurgical plans, to encompass embolization procedures [9, 13] and, more recently, staged volume treatments [36].

While the general consensus is that radiosurgical treatment of large AVMs results in lower obliteration rate with higher morbidity, published data are based on small groups and do not reflect on the evolving treatment strategies [19, 23]. We have treated over 4,350 AVM patients with more than 5,000 treatments since 1986, and 564 larger than 10 cm^3 were initially treated with single radiosurgical session. Since 2008, these lesions are exclusively treated with staged volume radiosurgery, and to establish a baseline for the current and future practice we analysed our historical material of single-stage treatments. We distinguished three evolutionary steps in treatment planning, from simplistic angiography-based plans to the addition of axial MRI. We explored whether improving radiosurgical planning improved outcome in terms of obliteration and side effects, and whether prior embolization added any benefit. Moreover, by analysing a patient population uniquely high in the literature harbouring large AVMs, we believe that this study may contribute significantly in the understanding of the natural history of large AVMs.

Patients and methods

Patient population

We analysed retrospectively patients with AVMs of at least 10 cm^3 treated with single-session gamma knife radiosurgery. Between 1986 and 2007, 564 patients underwent 699 treatments (which was approximately 14% of all AVM treatments performed in Sheffield during this period). There was a slight male prepondance (52%). Fifty-two percent of the lesions were left-sided, 46% right-sided and 2% midline. We followed Pollock and Flickinger [30] in the definition of eloquence: frontal, temporal (not invading the speech centres and the motor strip) are non-eloquent; fronto-parietal, speech, parietal, occipital, intraventricular, corpus callosum, cerebellar are intermediate; basal ganglia, internal capsule, thalamic and brainstem are considered eloquent (Table 1). Modified Spetzler-Martin grades [6, 38] were the following: 7% SMII, 43% SMIIIA, 1% SMIIIB, 47% SMIV, 2% SMV. Thirty percent of the patients had modified radiosurgery-based (Pollock-Flickinger) AVM score 1.5-2 and 70% had >2 [30, 31]. The median lesion volumes were 14.7 cm^3 (range: 10–55.9), and the median age at treatment was 35 years (range: 6–76). Previous surgical attempt was performed on 4%, and partial embolization on 27% of the patients.

Treatment details

Focus (KULA-based software modified in-house) was used for dose planning before 1994, and GammaPlan (Elekta, Stockholm, Sweden) thereafter. Treatment was initially carried out with the gamma knife model RBS 5000 (Nucletec, Geneva, Switzerland) which was replaced by Model C (Elekta, Stockholm, Sweden) in 2001. Stereotactic catheter angiography was performed for all treatments. MRI was gradually introduced for treatment planning of AVMs after 1999, and since 2001 no treatment was planned without axial imaging. Our standard marginal dose for AVMs is 25 Gy, and

Table 1 Localisation and presentation of large AVMs treated between 1985 and 2008 with gamma knife radiosurgery in Sheffield

		n	%
Location			
	Non-eloquent	74	13
	Frontal	39	7
	Temporal	35	6
	Intermediate	423	75
	Fronto-parietal	88	15.5
	Speech	26	4.5
	Sylvian	65	11.5
	Parietal	107	19
	Parieto-occipital	29	5
	Occipital	57	10
	Temporal (invading eloquent structures)	36	6.5
	Corpus callosum	5	1
	Cerebellar	10	2
	Eloquent	67	12
	Thalamus/basal ganglia	59	10.5
	Brainstem	8	1.5
Presentation			
	Haemorrhage		28
	Seizures		48
	Vascular steal		14
	Headaches		13
	Other[a]		1
	Combination		8
	Incidental		5

[a] Other presentation: thalamic tremor, benign intracranial hypertension, trigeminal neuralgia, exophtalmus

we generally consider a 2.5-Gy reduction for large lesions, if the lesion is eloquently sited, for patients younger than 16 years, and for patients previously undergoing radiotherapy, but we are reluctant to reduce the dose below 17.5 Gy [22]. Several conceptual changes have been introduced in the treatment of large AVMs since 1985, which is discussed—together with detailed treatment parameters—in "Results".

Follow-up

The follow-up protocol has essentially been unchanged during the last 20 years: most importantly, we still consider catheter angiography as the "gold standard" for the demonstration of a cure. According to our current protocol, we first recommend to perform an MRI and MRDSA 2 years after treatment [3, 27], and if there is an indication of full obliteration, angiography is performed at 2 years. If persisting nidus is demonstrated on MRI scanning, catheter angiography is performed 3–4 years after treatment and patients with persisting nidus are scheduled for further treatment after 4 years. We obtained complete radiological follow-up from 400 patients at 4 years, and useful clinical follow-up information (including earlier imaging only) from 492 patients.

We graded obliteration response with the following grades: 0–1, no detectable changes or only minimal changes; 2, partial response with substantial reduction in nidus size (including "near total" obliteration—persisting early draining vein with or without hardly detectable nidus); 3, residual pathological vessels visible without early draining vein; 4, complete disappearance of pathological vessels (both 3 and 4 are considered safe, as described [22]).

Annual haemorrhage rates were calculated by dividing the number of haemorrhages with the number of observation years. Post-treatment haemorrhage rates for non-obliterated AVMs were counted with the follow-up years from the treatment to the last available clinical information. For obliterated AVMs, we used an average post-treatment year estimated from the last known non-obliterated state and the first detection of obliteration with the assumption that AVMs do not fully obliterate within the first year after treatment (e.g. if an AVM was shown to be obliterated 2 years after treatment, we calculated 1.5 years, and if the 2-year follow-up image showed residual nidus but the 4-year angiogram demonstrated obliteration, we calculated 3 years).

Permanent morbidity was measured with the modified Rankin scale (MRS): 0, no symptoms at all; 1, no significant disability despite symptoms—able to carry out all usual duties and activities; 2, slight disability—unable to carry out all previous activities but able to look after their own affairs without assistance; 3, moderate disability—requiring some help but able to walk without assistance; 4, moderately severe disability—unable to walk without assistance and unable to attend to their own bodily needs without assistance; 5, severe disability—bedridden, incontinent and requiring constant nursing care and attention [46]. We used Mann–Whitney *U*, Kruskal-Wallis, and Fisher's exact tests for statistical analysis, and 95% confidence intervals (CI) are given, as appropriate.

Results

Evolving radiosurgical treatment strategies for large AVMs and prior embolization

Since 1986, several major conceptual changes have been introduced in the treatment planning of large AVMs. Between 1986 and 1993, plans were based on catheter angiography only; they were simplistic, using a median of 2 isocentres (range 1–5); the lesions were under-treated in terms of volume, with higher marginal dose; therefore, we called this group "non-conformal" angio planning (Figs. 1a, b, 2a and Table 2). A more conformal, yet still catheter-angiography-based planning was gradually introduced and dominated our planning from 1994 to 2000. During this period plans became more sophisticated, using a median of 5 isocentres (range 2–14), covering a larger percentage of the lesion with a lower marginal dose; therefore we called this group "conformal" angio planning (Figs. 1c-d, 2b and Table 2). Since 1999 (and exclusively after 2001) MRI has been used systematically in combination with angiography (we simply call it "MRI planning"), median isocentres increased to 7 (range 3–25) and the coverage of AVMs and marginal dose appeared to be similar to "conformal" angio planning (Figs. 1e-h, 2c and Table 2). The most recent development is staged volume radiosurgery [34], which has been being increasingly used since 2006 and is not included in the present study. We treated 157 AVMs with "non-conformal" angio planning, 223 with "conformal" angio planning and 182 with MRI planning.

Partial embolization prior to radiosurgery became increasingly popular: only 9% of the AVMs were embolized in the earliest, "non-conformal" angio group, 28% in the "conformal" angio group and 44% of the AVMs in the MRI group. The rationale behind prior embolization is to achieve segmental volume reduction [9, 13]. However, clear segmental volume reduction is not always possible, and treatment planning for some of the pre-embolized AVMs becomes extremely difficult (Fig. 3); therefore, we also analysed the effect of prior embolization on the outcome after radiosurgical treatment.

Presentation, pretreatment haemorrhages, and morbidity

The median age at presentation (diagnosis) was 29 years (range: 2–75). Only 28% of the AVMs presented with bleeding

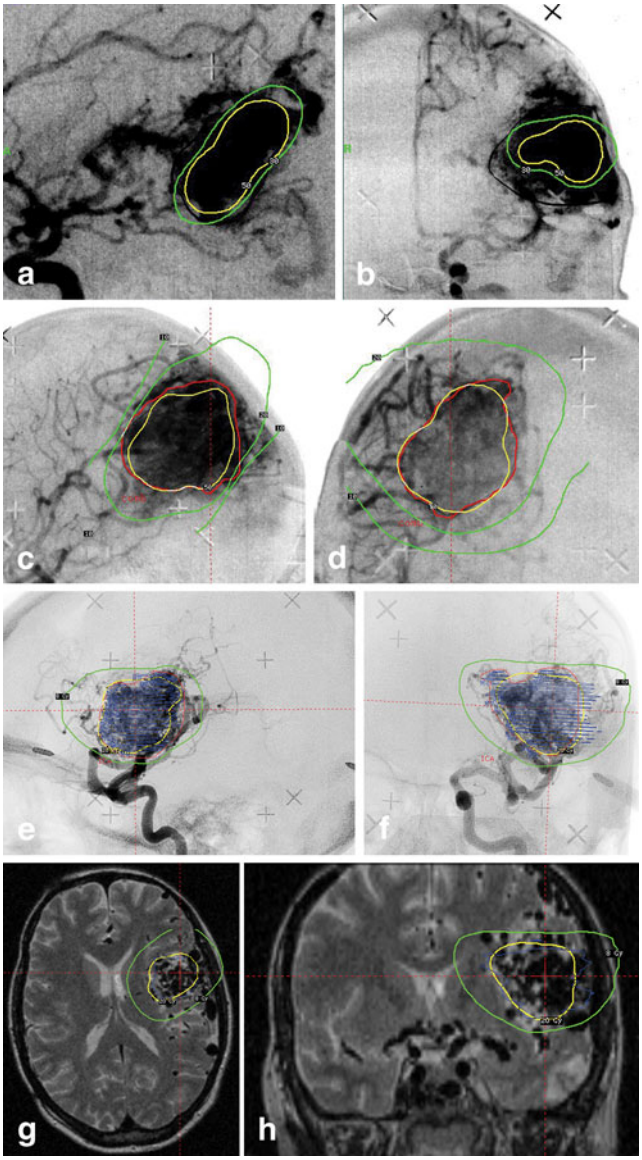

Fig. 1 Historical stages of the treatment of large AVMs. **a**, **b** Until 1993, plans were simplistic, using few isocentres; the plan was based on angiography ("non-conformal" angio plans). **c**, **d** Angiography based plans became more conformal after 1994, using more isocentres, covering a larger proportion of the AVM ("conformal" angio plan). **e-h** More recently, axial imaging (MRI) has been introduced to achieve the highest conformality. *Red* target outlined on angiography; *blue* target outlined on MRI; *yellow* 50% isodose line; *green* isodose lines <50% as indicated

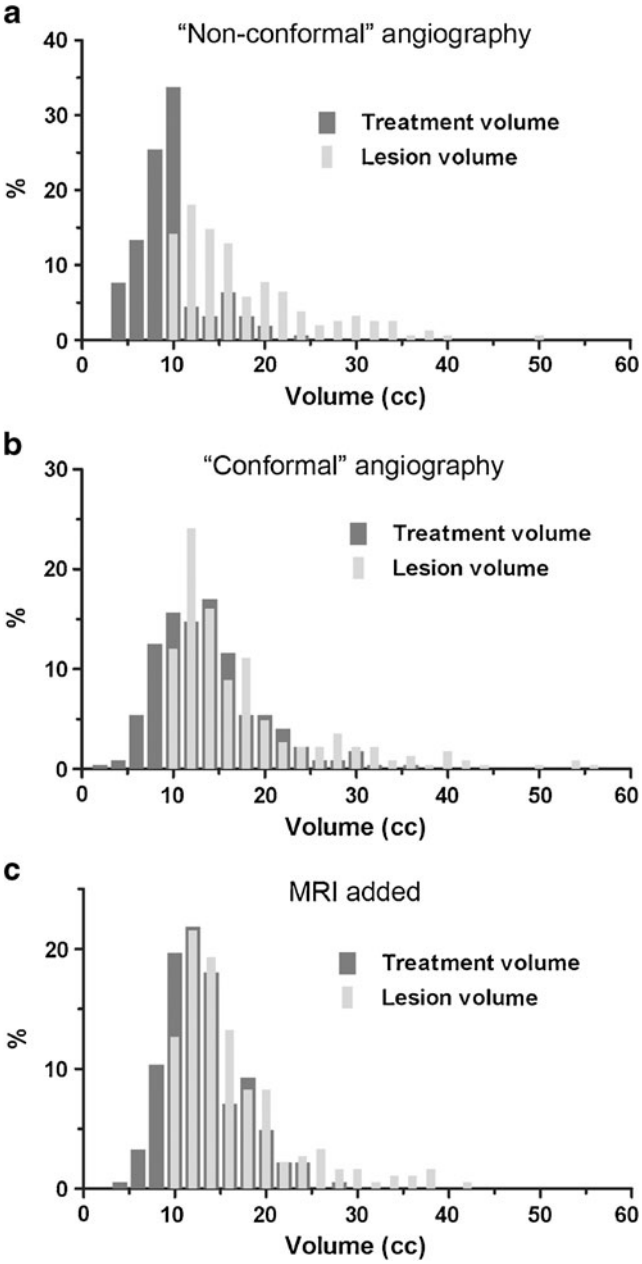

Fig. 2 Frequency distribution of treatment and lesion volumes of the "non-conformal" angiography-based treatments (**a**), the "conformal" angiography-based treatments (**b**) and the MRI-based treatments (**c**)

(Table 1), and 39% of these patients suffered from permanent morbidity (42% of non-eloquent, 33% of intermediate, 55% of deep-eloquent). Similarly, 42.5% of the patients with vascular steal had fixed neurological deficit by the time of treatment, but only 7.5% of the patients originally presented with seizures had developed a fixed neurological deficit without bleeding until treatment (Fig. 4). Thirty-two percent of the patients undergoing prior embolization had permanent neurological deficits, and one-fifth of these was related to embolization.

The median time between presentation and treatment was 2 years (range: 0.5-40), both in the haemorrhagic and in the unruptured groups. Some of the initially unruptured lesions had bled during this time period (altogether 31% of the patients suffered from haemorrhage until treatment, 29% of those with hemispheric and 61% of those with deep-eloquent AVMs). This delay between diagnosis and treatment allowed us to calculate retrospective (i.e. until diagnosis) and prospective (i.e. between diagnosis and radiosurgical treatment) haemorrhage rates.

Table 2 Treatment parameters in different subgroups (mean ± SD, and median, range for isocentres)

		NC-angio	C-angio	MRI
10-12 cm^3	Lesion (cm^3)	10.9±0.5	11±0.6	10.9±0.6
	Treatment (cm^3)	7.7±2	10.5±3.3	10.2±2
	PITV	0.71	0.95	0.94
	Margin dose (Gy)	23.9±1.9	21.3±2.2	21.7±1.4
	Peak dose (Gy)	48.3±4.6	43.1±4.4	43.3±2.8
	Isocentres	2, 1-4	5.5, 2-10	9, 4-16
12-20 cm^3	Lesion (cm^3)	15.3±2.2	15.1±2.3	15.4±2.4
	Treatment (cm^3)	8.8±2.5	12.5±3.7	13±3.6
	PITV	0.58	0.83	0.84
	Margin dose (Gy)	23±2.9	21.1±3.3	21.1±1.6
	Peak dose (Gy)	46.7±6.4	41.8±4.9	42.1±3.1
	Isocentres	2, 1-5	6, 2-14	9, 3-23
>20 cm^3	Lesion (cm^3)	27.4±6.4	30.8±9	27.7±6.2
	Treatment (cm^3)	12.3±4.3	19.8±6.6	17.2±4.8
	PITV	0.45	0.64	0.62
	Margin dose (Gy)	22.2±3.7	19.4±2.3	20.5±1.3
	Peak dose (Gy)	46.8±7.9	39.7±4.5	41±2.7
	Isocentres	3, 1-5	7, 3-13	10, 5-25

NC-angio non-conformal angio plan, *C-angio* conformal angio plan, *PITV* treatment volume (prescription isodose) divided by lesion (target) volume [37]

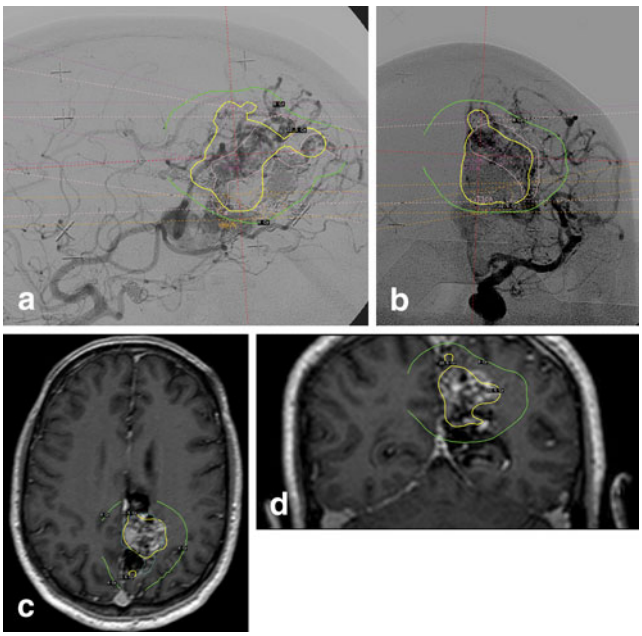

Fig. 3 Prior partial embolization might make radiosurgical treatment planning extremely complex and difficult. **a, b** Left internal carotid artery filling with projections of different components of the residual nidus filled by right internal carotid and vertebral arteries (indicated with *dotted lines of different color coding*). **c, d** Post-gadolinium T1 weighted MRI images show the overlapping embolized (hypointense) and non-embolized (hyperintense, contrast-enhancing) parts of the nidus

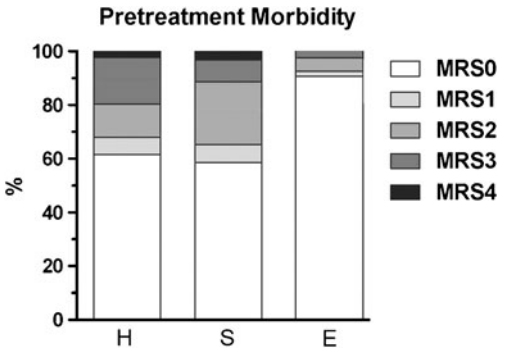

Fig. 4 Natural history of large AVMs: pretreatment morbidity in the main presentation groups quantified by the modified Rankin scale (MRS, [46]). *H* hemorrhagic presentation, *S* vascular steal, *E* seizures

Annual haemorrhage rates are summarized in Table 3. In deep-eloquent AVMs both retrospective (odds ratio: 1.96, CI: 1.26-3.06, $p<0.01$) and prospective (odds ratio: 12.5, CI: 5.2-30.3, $p<0.0001$) haemorrhage rates were significantly higher than in hemispheric AVMs. Similarly, the rebleed rate of deep-eloquent AVMs was significantly higher than of hemispheric AVMs (odds ratio: 2.8, CI: 1.7-4.5, $p<0.0001$).

Increasing size did not change bleeding rates (data not shown).

Obliteration

At 2 years, "non-conformal" angio planning resulted in obliteration in 15% of the treated AVMs ($n=139$), "conformal" angio planning 19% ($n=200$) and MRI planning 27% ($n=102$). This was increased by 4 years to 27% with "non-conformal" angio planning ($n=119$), 30% with "conformal" angio planning ($n=185$) and 53% with MRI planning ($n=81$) (Fig. 5a). MRI planning significantly increased obliteration at 4 years ($p<0.0001$, post test: $p<0.001$ versus "non-conformal", and $p<0.01$ versus "conformal" angio planning).

Prior embolization significantly reduced obliteration rate: it was 38% (113 out of 299) without prior embolization, and 26% (25 out of 97) with prior embolization ($p<0.05$). The detrimental effect of prior embolization was consistently seen in all three treatment planning groups (Fig. 5b), most prominently in the MRI group: MRI without prior embolization almost doubled obliteration rate ($p<0.05$).

In order to determine the effect of size on obliteration, we constructed three clinically useful size groups: 10–12, 12–20, and >20 cm^3 (Table 2). Obliteration rates in "non-conformal" angio group were 39, 25, and 21% ($n=31$, 61 and 32); in "conformal" angio group 46, 32, and 22% ($n=37$, 101 and 51); and in MRI group 76, 52, and 29% ($n=17$, 50 and 17).

Table 3 Natural history of large AVMs: annual haemorrhage rates before the first radiosurgical treatment

	Retrospective first ever	Prospective first ever	Rebleed
Total	0.88%, CI: 0.73-1.03 (138 bleeds in 15,638 years)	1.05%, CI: 0.6-1.5 (21 bleeds in 1,956 years)	8.85%, CI: 7–10.7 (80 bleeds in 902 years)
Hemispheric	0.8%, CI: 0.65-0.95 (111 bleeds in 14,082 years)	0.65%, CI: 0.3-1 (12 bleeds in 1,828 years)	6.55%, CI: 4.7-8.4 (46 bleeds in 701 years)
Deep eloquent	1.5%, CI: 0.9-2.1 (24 bleeds in 1,556 years)	7%, CI: 2.5-11.5 (9 bleeds in 128 years)	16.4%, CI: 11.2-21.6 (32 bleeds in 195 years)

Importantly, even in lesions larger than 12 cm^3 60% obliteration was achieved if no embolization was done before (Table 4).

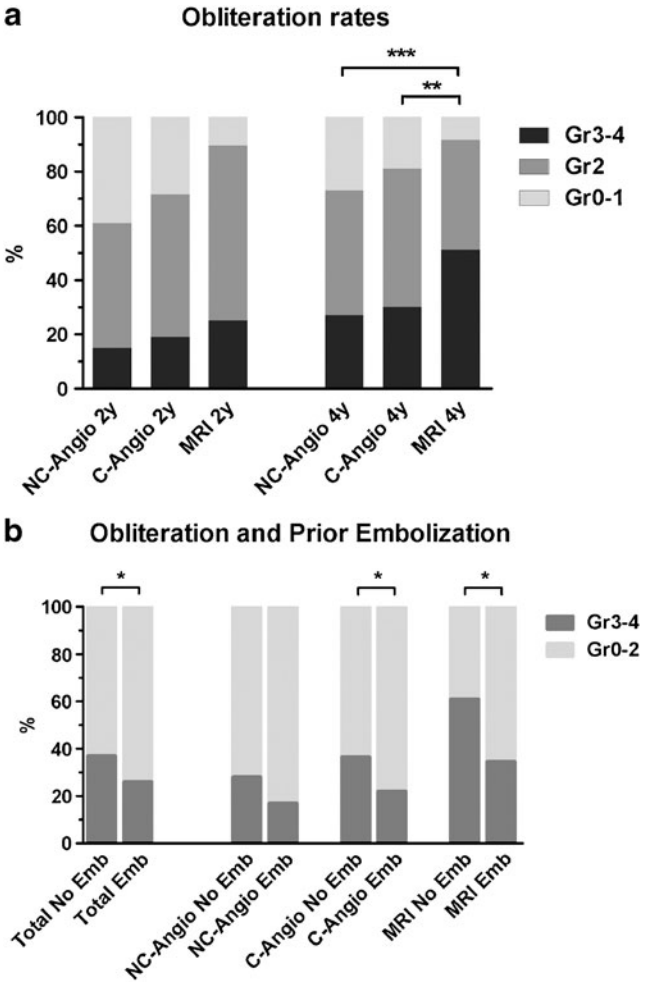

Fig. 5 The effect of treatment planning on obliteration rates of large AVMs. (**a**) The effect of conformality by using "non-conformal" angio plan (*NC-Angio*), "conformal" angio plan (*C-Angio*) and *MRI*. The *left panel* shows obliteration at 2 years, and the *right panel* shows obliteration at 4 years after radiosurgery. The introduction of MRI-planning significantly increased obliteration rates at 4 years after radiosurgery. Gr0-1 (*light grey*): no or hardly any response, Gr2 (*grey*): partial response, Gr3-4 (*black*): obliterated, no early draining vein is visible. (**b**) Prior embolization significantly reduces obliteration. This effect is seen in all three historical planning groups, most prominently in the MRI planning group (*$p<0.05$, **$p<0.01$, ***$p<0.001$)

Adverse radiation effects

The rate of temporary adverse radiation effects was the highest in the MRI group, although not significantly (8% in "non-conformal" angio planning, 11% in "conformal" angio planning, and 16% in MRI planning). However, the rate of permanent adverse radiation effects ≥MRS2 was the highest in the "non-conformal" angio group, though the difference was not significant (14% in "non-conformal" angio planning, 9% in "conformal" angio planning, and 9% in MRI planning). There was a tendency to increased rate of more severe permanent radiation effects with older planning, increasing size and eloquence (Tables 5 and 6).

Haemorrhages after treatment

The post-treatment first-ever haemorrhage rate was 3.6% in previously unruptured AVMs (48 bleeds in 1,342 years, CI: 2.6-4.6), and the post-treatment rebleed rate was 6.6% (51 bleeds in 771 years, CI: 4.8-58.4). In unruptured AVMs, the bleeding risk was significantly higher after radiosurgical treatment (odds ratio: 3.4, CI: 2–5.7, $p<0.0001$), whereas the rebleed rate was not significantly different (odds ratio: 0.73, CI: 0.5-1.05, $p=0.1$) (Fig. 6a). No difference was found between different treatment plans, and prior embolization did not change post-radiosurgical bleeding rates either (data not shown).

Post-treatment bleed rates increased within the first 2 years after radiosurgery in the previously unruptured AVMs and fell in the third year, whereas rebleed rate remained high

Table 4 Obliteration rate (%), size, and prior embolization. Because of the low number of embolized patients in the non-conformal angio group, only conformal angio (*C-angio*) and MRI based planning are presented

	C-angio		MRI	
	Non-embolized	Embolized	Non-embolized	Embolized
10-12 cm^3	54 (28)[a]	29 (7)	75 (12)	80 (5)
12-20 cm^3	34 (70)	27 (29)	58 (31)	39 (18)
>20 cm^3	28 (36)	11 (18)	62 (8)	0 (9)

[a] Number of patients in each group

Table 5 The rate of adverse radiation effects in different size and planning subgroups

	10-12 cm^3	14-20 cm^3	>20 cm^3
NC-angio (*n*)	(32)	(65)	(44)
Temporary	3	11	7
-MRS1[a]	3	4.5	7
-MRS2	6	3	7
-MRS3	3	6	13.5
-MRS4	0	0	4.5
C-angio (*n*)	(44)	(104)	(55)
Temporary	13.5	9	13
-MRS1	2.3	5	2
-MRS2	7	4	5.5
-MRS3	4.5	1	3.5
-MRS4	0	0	0
MRI (*n*)	(34)	(66)	(24)
Temporary	17.5	15	17
-MRS1	6	6	8
-MRS2	6	4.5	8
-MRS3	0	4.5	4
-MRS4	0	0	0

[a] Permanent deficits are indicated as decline in modified Rankin scale (−*MRS*)

Table 6 The rate of adverse radiation effects in different planning subgroups depending on eloquence

	Non-eloquent	Intermediate	Eloquent
NC-angio (*n*)	(14)	(92)	(35)
Temporary	14	10	0
-MRS1[a]	0	5.5	6
-MRS2	0	3	11.5
-MRS3	0	5.5	17
-MRS4	0	0	6
C-Angio (*n*)	(31)	(154)	(18)
Temporary	6.5	11	16.5
-MRS1	6.5	2.5	5.5
-MRS2	0	7	11
-MRS3	0	2	11
-MRS4	0	0	0
MRI (*n*)	(17)	(97)	(10)
Temporary	6	17	20
-MRS1	6	6	10
-MRS2	0	7	0
-MRS3	0	3	10
-MRS4	0	0	0

[a] Permanent deficits are indicated as decline in modified Rankin scale (−*MRS*)

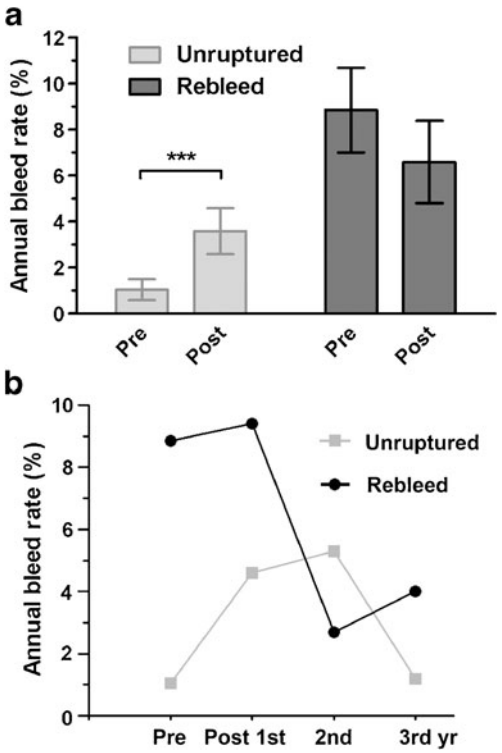

Fig. 6 Comparison of bleeding rates before and after radiosurgery. **a** *Light-grey bars* show the mean (±95% CI) prospective annual rates of first-ever bleed in unruptured AVMs before and after treatment, and *dark-grey bars* the rebleed rates before and after treatment (***$p<0.001$). **b** First-ever bleed rates increased to 4.6 and 5.3% in the first and second post-treatment years, falling to 1.2% in the third post-treatment year (*light grey*), whereas rebleed rate was high only within the first post-treatment year in the previously ruptured AVMs (9.4%) and fell to 2.7 and 4% in the second and third post-treatment years (*black*)

only in the first post-treatment year in the previously ruptured AVMs and fell subsequently (Fig. 6b).

Outcomes after the first radiosurgical treatment

The outcome of radiosurgery depends on obliteration and permanent morbidity caused either by radiation or post-treatment haemorrhages (Tables 5, 6, 7). We used a standardized outcome scale with six grades depending on obliteration and the severity of neurological deficit as described [34]. Based on this scale, the most optimal planning group is MRI planning without prior embolization with about 60% excellent or good outcome (Fig. 7).

Interestingly, outcomes did not depend on SM grade in the angio planning groups (data not shown), whereas in the MRI group the rate of excellent/good outcomes decreased with SM grade (SMII-III: without prior embolization 77%, and 56% with prior embolization; SMIV-V: 46% without prior embolization, and 24% with prior embolization). We found the modified Pollock-Flickinger AVM score less predictive, especially in the MRI group (excellent/good outcome

Table 7 Rates of permanent morbidity—indicated as decline in modified Rankin scale (−*MRS*)—and mortality caused by post-treatment haemorrhages in different subgroups

	Non-eloquent	Intermediate	Eloquent
NC-angio (*n*)	(14)	(95)	(35)
-MRS1	0	0	3
-MRS2	0	0	0
-MRS3	7	3	3
-MRS4+	0	1	0
Mortality	7	7.5	11
C-angio (*n*)	(31)	(155)	(18)
-MRS1	0	0	0
-MRS2	0	2	5.5
-MRS3	0	1	0
-MRS4+	0	0	0
Mortality	10	8	11
MRI (*n*)	(18)	(98)	(10)
-MRS1	0	0	0
-MRS2	0	3	10
-MRS3	0	0	0
-MRS4+	0	1	0
Mortality	5.5	1	0

was found in 52% of the AVMs with scores 1.5-2, and in 46% of the score >2 group). Specifically, we found no correlation between age and outcome, which was one of the variables related to outcomes, along with size and location in the Pollock-Flickinger AVM score [30, 31].

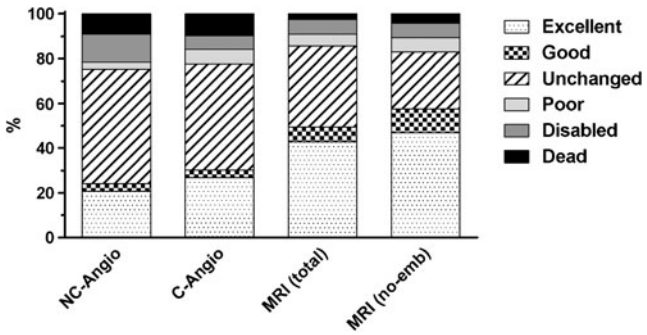

Fig. 7 Patient outcomes after the first radisorurgical treatment of large AVMs treated with different planning. The introduction of MRI (*n*=77) markedly improved the rate of excellent/good outcomes, and the highest rate of good/excellent outcomes can be achieved if patient had not had prior embolization (*n*=47). (*NC-Angio*: "non-conformal" angio plan, *n*=121; *C-Angio*: "conformal" angio plan, *n*=183) Outcomes are adapted from Pollock et al. [34]. *Excellent*: complete obliteration without permanent new neurological deficit. *Good*: complete obliteration with new permanent minor neurological deficit. *Unchanged*: incomplete obliteration without new permanent neurological deficit. *Poor*: incomplete obliteration, new permanent minor neurological deficit. *Disabled*: new permanent major neurological deficit that interferes with the patient's preoperative level of functioning, regardless of obliteration

Further treatments

Second radiosurgical treatment was performed on 123 patients (50% of the non-obliterated AVMs) with 64% obliteration rate (48 out of 75 patients). Both temporary (2%) and permanent adverse radiation effects (1% MRS1, 2% MRS2, 3% MRS3) were rare. In the previously unruptured group a temporary increase of bleed rates was observed within the first 2 years after the second radiosurgical treatment, similar to the increase observed after the first treatment. Eleven patients had a third radiosurgical treatment, and all four of these patients with follow-up angiography underwent obliteration without side effects.

Surgical removal of residual AVMs was attempted on 18 patients (7%), and 48 (19%) patients underwent post-radiosurgical embolization [14]. Six patients had both post-radiosurgical embolization and surgery, and three patients had embolization followed by further radiosurgery.

Mortality

During the follow-up, 35 patients died related to their AVM, exclusively due to haemorrhage (Table 7). Mortality was the least frequent in the MRI group. However, it may not represent a true reduction in mortality, since this is the most recent group with the shortest follow-up period of non-obliterated AVMs.

Treatment parameters and outcome

Larger and more eloquent lesions were under-treated with lower marginal doses and smaller treatment volumes in all historical planning groups (see Table 2). However, we did not find significant correlation between treatment parameters and outcomes (both in terms of obliteration and side effects, data not shown).

Discussion

Natural history of large AVMs

The annual bleeding rate of AVMs is estimated between 2 and 4% [4, 5, 10, 14, 33, 42]. There is a general consensus that prior haemorrhage—especially within the first 5 years—and deep location are independent risk factors for bleed [8, 10, 14, 26, 33]. More conflicting is the relationship between size and bleeding. Some argue that smaller size is associated with higher feeding artery pressure and therefore higher haemorrhage risk [40], while others did not find a relationship between size and bleeding rate [5, 42, 45], or even demonstrated increased bleeding risk associated with large size [14, 18, 25].

The annual first-ever haemorrhage rate in our material was low, 0.88% until diagnosis and 1.05% between diagnosis and treatment in the previously unruptured group. However, the annual rebleed rate was significantly higher, 8.85%. Rebleed rate remained high until treatment, but notably the time between the first bleed and treatment was relatively short (median of 2 years). Deep-eloquent location significantly increased bleeding rate in all aspects: the annual rate of first-ever haemorrhage until diagnosis was 1.5% (versus 0.8% for hemispheric AVMs), 7% (versus 0.65%) between diagnosis and treatment, and the rebleed rate was 16.4% (versus 6.55%). These data support recently published findings [14, 18]. However, our data are based on a more robust patient population with large AVMs (564 patients) providing 20,450 patient years of observation until treatment. Of note, we miss those patients who died or became severely disabled due to the first bleed or rebleed before radiosurgical treatment, and also miss those patients who underwent successful obliteration with other treatment modalities, therefore our results may slightly underestimate bleeding rates. This may also explain why our data do not demonstrate increased rebleed rate within the first post-haemorrhage year (7% during the first post-bleed year versus 8.85% during the whole first bleed-treatment interval).

Having a low annual first-ever haemorrhage rate and being large in size, it is not surprising that only 28% of these AVMs presented with haemorrhage (Table 1). This confirms previous observations that the proportion of hemorrhagic presentation is higher in smaller than in larger AVMs [20, 42]. Our data put the first-ever haemorrhage rate of large AVMs below the generally accepted 2–4%, in agreement with Han et al. [11]. However, a massive increase in haemorrhage rate is observed once the lesion has bled, indicating that once these AVMs become hemodynamically unstable they are more likely to bleed repeatedly. Interestingly, unruptured deep-eloquent AVMs have increased bleeding rate after diagnosis, suggesting that presenting symptoms (neurological deficit and/or seizures) may be indications of haemodynamic instability and therefore may be considered as warning signs in this particular location. In this context, our observed increase of haemorrhage rate after radiosurgery may not be fully attributable to the treatment but to this developing instability (see below).

Management strategies for large AVMs and the role of radiosurgery

The primary goal of AVM treatment is the elimination of bleeding risk with morbidity lower than the morbidity of bleeding. It is generally accepted that, in order to eliminate bleeding risk, complete elimination of the pathological shunt is required [12, 29]. Based on this principle, we only consider an AVM "cured" if the early draining vein is absent (grade 3 or 4 response, see "Patients and methods") and it is therefore recommended to offer further treatment in the case of subtotal obliteration. In the present series, 50% of the non-obliterated AVMs underwent further radiosurgical treatment, 7% residual were resected, 19% embolized and a few cases required multimodality treatment reflecting on the heterogenity of the cases that require individually based management strategies.

Because of the high treatment-related morbidity and low cure rate the role of active treatment in the management of large (SMIV and V) AVMs is debated [2, 6, 18, 38, 39]. Surgery carries high risk even in experienced hands [39], and endovascular treatment rarely provides a cure despite high morbidity rate, even with newer embolization materials like Onyx [17]. A single radiosurgical session is considered to result in a low cure rate with high morbidity by some [12, 16, 19, 22, 30] and, therefore, radiosurgery is generally not recommended for lesions larger than 3 cm in diameter (or a volume of 10 cm^3) by most centres [29]. If treated, single treatment modalities often do not yield a complete cure and thus multimodality treatment is needed [2, 18].

Several strategies have been published to determine the optimal role of radiosurgery in the management of large AVMs. Firstly, it may be used as part of a multimodality approach. Radiosurgery can be used as first treatment and if residual nidus is left after a single radiosurgical session, it can be treated either by surgery [43], by embolization [15] or by repeat radiosurgery [21]—as it is also reported in the present paper. Secondly, the currently popular embolization aims to improve outcome by reducing nidus size prior to radiosurgery [9, 13, 29]. Recently, staged volume radiosurgery offers promising alternative as a single modality treatment [36]. The problem is that large AVMs are rare, and either constitute only a small proportion of even large radiosurgical series or publishing them separately the series are small [19, 23].

In the present study we reviewed our historical material of single-stage radiosurgical treatment of large (≥10 cm^3) AVMs and demonstrated that improving planning techniques significantly improved outcome. Three distinct developmental stages of radiosurgical treatment are identified. Before 1993, radiosurgical plans were simplistic, non-conformal, based on angiography only using higher marginal doses; between 1994 and 2000, plans were still based on angiography only but became more sophisticated with increasing conformality, using lower marginal doses; and between 2000 and 2007, MRI has been used in combination with angiography providing the highest conformality (Fig. 1, Table 2). The introduction of MRI significantly increased obliteration rate after a single radiosurgical session (from 27 to 52%, Fig. 5a), but adverse radiation effects (≥MRS2 14% in "non-conformal" angio planning, 9% in "conformal" angio planning, and 9% in MRI planning), and post-treatment bleeding rates remained

similar. With better planning the complications tended to be more temporary and less severe.

Twenty-seven percent of the patients underwent previous partial embolization. The increasing popularity of embolization is reflected in our material: lately almost half had undergone such treatment. While it sounds theoretically attractive, recent data have challenged this practice, reporting decreased obliteration rate after prior embolization [1]. This observation is supported by our material: prior embolization reduced obliteration rate (Fig 5b and Table 4) without providing any benefit in terms of reducing side effects and post-treatment haemorrhage rates. Most notably, obliteration was only 36% with and 61% without prior embolization with contemporary treatment planning. The reason for this disappointing effect of prior embolization on obliteration is speculated to be due to a more complicated and, therefore, inaccurate treatment planning (Fig 3), radio-opacity of the glue, or recanalization. Moreover, 6.4% of pre-radiosurgery morbidity was accounted to embolization (embolization related procedural risk was 20%). Embolized AVMs may of course be a subgroup particularly difficult to treat, and it is also possible that we missed those lesions in which prior embolization successfully achieved significant partial volume reduction (i.e. lesion volume became <10 cm^3), because our selection criteria for this study was lesion volume at radiosurgical treatment. Nevertheless, we think these data draw attention to the drawbacks of prior embolization and hopefully will promote the involvement of radiosurgeons in multimodality treatment planning from the very beginning of the management of a newly diagnosed AVM.

Detailed analysis of our contemporary material (Tables 4 and 5) suggests that a size of 12 cm^3 may be decisive in terms of radiosurgical outcome. Of note, we found a similar cut-off, 4–6 cm^3, in deep highly eloquent lesions [28]. The other contributing factor to outcome is eloquence: the development of disabling side effects (MRS ≥3) increases with eloquence (0% in non-eloquent, 3% in intermediate, and 10% in eloquent location in the MRI group, Table 6).

There is an active debate on whether it is justified to offer radiosurgery to treat large AVMs at all. Opponents of radiosurgery often argue with the published disappointing results, while continued evolution of radiosurgical techniques always gives radiosurgeons new hope to improve upon these old results. The aim of this study was to demonstrate the technical development and its impact on outcomes of single-stage radiosurgery and to set a baseline for future development. As historical material it does not represent our current practice (staged volume radiosurgery), but it is important to see what the development of radiosurgical technique was able to achieve in the treatment of large AVMs in the past and to place it in the context of the present. In this study we demonstrated that an acceptable cure rate (60% with one session, and another ~60% with a repeat session) can be achieved with single-stage radiosurgery in AVMs >12 cm^3 under optimal treatment conditions (addition of axial imaging to planning and without prior embolization), but persisting radiation-induced morbidity remained high (18%) and bleeding during latency period seems to be a bigger problem than in smaller AVMs [7, 32]. Early results of staged volume radiosurgery suggest similar obliteration rate (50%), a reduction of radiation induced morbidity (4%), but no improvement in post-treatment bleeding rate [36]. In our opinion, radiosurgery offers a real treatment alternative in the management of large AVMs.

Ruptured versus unruptured large AVMs

Thirty-nine percent of the patients harbouring previously ruptured large AVMs referred for radiosurgery suffered from persisting neurological deficits (20% disabling, ≥MRS3) and annual rebleed rate is increased from 1% first-ever haemorrhage rate to 8.85%. While radiosurgery does not significantly change the rebleed rate in the first post-treatment year, the rebleed rate drops dramatically thereafter (Fig 6). Therefore, the long-term benefits make it a treatment alternative for otherwise untreatable ruptured AVMs, and this may be even more so with the reported low morbidity rate of staged interventions. Similarly, once a previously unruptured, large, deep, eloquent AVM is diagnosed, annual first-ever bleed rate appears to increase from 1.5 to 7% without treatment, which might justify a more active management.

The management dilemma is greatest for the unruptured hemispheric AVMs [41]. The annual rate of first-ever haemorrhage of these AVMs was found to be relatively low, <1%. Thus, the lifetime risk of haemorrhage in a patient diagnosed with unruptured large AVM at age 35 is estimated to be <35% [24], which has recently been confirmed by a retrospective observational study on large AVMs (24% 20-year rupture rate, and 23% AVM-related mortality within a mean follow-up of 11 years) [25]. This risk and the resulting morbidity/mortality of untreated unruptured AVMs should be weighed against the significant temporary increase of bleeding rate after radiosurgery (4.6 and 5.3% in the first and second post-treatment years) and a relatively low treatment-related morbidity with the current technique [36].

Conclusions

Despite advances in radiosurgical treatment planning, single-session radiosurgical treatment of large AVMs results in lower obliteration rates with higher morbidity than the treatment of smaller AVMs. Based on the current study, single-stage radiosurgical treatment of hemispheric AVMs larger than 12 cm^3 is questionable. The introduction of MRI planning significantly

increased obliteration rates, but without significant reduction of persisting adverse radiation effects and post-treatment haemorrhage rates. Prior embolization reduces eventual cure rate, therefore the involvement of radiosurgeons in patient selection before partial embolization is advised. Recently, staged volume radiosurgery has become increasingly popular in the treatment of large AVMs. It will be interesting to see in large series whether this new technique fulfills the hopes based on the initial reports and is able to improve outcome in comparison with this historical material.

Conflicts of interest None.

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