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Arteriovenous malformations

Clinical outcome after repeated radiosurgery for brain arteriovenous malformations

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ABSTRACT

Introduction: We assessed the clinical and radiological outcome after repeated radiosurgery for brain arteriovenous malformations (bAVMs) after failure of initial radiosurgery.

Materials and methods: Fifteen patients underwent repeated radiosurgery. The mean bAVM volume at first radiosurgery (S1) was 4.6 ± 4.3 ml and that at second radiosurgery (S2) was 2.1 ± 2.5 ml. The median marginal dose was 18 Gy at S1, and 21 Gy at S2. Modified Rankin Scale (MRS) score was determined in all patients at last follow-up (FU).

Results: Complete obliteration was reached in nine patients (60%). Median time to obliteration was 50 months after S2. An excellent outcome (no new neurologic deficiencies, complete obliteration) was reached in seven patients (47%). Eleven patients (73%) showed a MRS $\leqslant$ 1. Radiation-induced complications occurred in 20%, of which 13% occurred after S2. Radiological complications included cyst formation ($n = 1$), radiation-related edema ($n = 4$), and radiation necrosis ($n = 1$), resulting in an increasing mean MRS of 0.5 at S1, 0.6 at S2, to 0.8 at FU. No (re-)bleedings were encountered during 137-patient years at risk.

Discussion: Repeated radiosurgery is a viable option for the treatment of small remnant bAVMs. We report 20% permanent radiation-induced complications. Such complications were mainly seen in relatively large, and therefore difficult to treat, bAVMs.

The goal in the treatment of brain arteriovenous malformations (bAVMs) is complete obliteration or resection without inducing new neurological deficits [1]. Using radiosurgery this goal is reached in 67–81% after 4 years and in 87–91% after 5–6 years [2–5]. Although failure analyses report several causes for treatment failure, i.e.: inadequate nidus definition, intentional partial irradiation, large nidus volume, suboptimal radiation dose, recanalization or re-expansion of the nidus, and radioresistance associated with an intranidal fistula [6–9], the appropriate treatment after incomplete obliteration has not been addressed extensively.

Previous studies have demonstrated that the chance of successful obliteration after repeated radiosurgery, in case of failure of initial radiosurgery, may be comparable to that of the initial radiosurgery, with reported obliteration rates varying between 35% and 86% [10–14]. However, as the complication rate increases with the amount of radiation previously given [14], we have evaluated our performance and the clinical outcome in 15 patients with a bAVM who were submitted to repeated radiosurgery after failure of the initial radiosurgical procedure.

Materials and methods

Between January 1991 and December 2007, 312 radiosurgical procedures for the treatment of one or more angiographically visible bAVMs were carried out in the VU University Medical Center (Amsterdam, The Netherlands). Seventeen of these procedures were salvage treatment for previously unsuccessfully radiosurgically treated bAVMs.

Our treatment regimen has been published previously [15]. In summary, unruptured bAVMs $\leqslant$3.5 cm are treated by radiosurgery. Larger bAVMs undergo endovascular embolization, and if this results in a residual nidus $\leqslant$3.5 cm, radiosurgery may follow. Ruptured bAVMs, or bAVMs that demonstrate angiographic characteristics suggestive of an increased (re-)bleeding rate, such as intranidal aneurysms [16], are always treated endovascularly first.

Patients were examined with MR imaging of the brain using a 1.5 T whole-body scanner, with a standard polarized head coil (Magnetom Vision, Magnetom Sonata; Siemens, Erlangen, Germany). T2-weighted MR images with a slice thickness of 3 mm, as well as Time-of-Flight MRA images with a slice thickness of 2 mm were acquired. MR imaging was usually performed 1 day prior to radiosurgery. On the day of radiosurgery, a stereotactic

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base ring (BrainLAB AG, Feldkirchen, Germany) was placed on the patient's head under local anesthesia. Digital subtraction angiography (DSA) and 2 mm sliced planning CT angiography scans were made with the stereotactic frame in situ. The DSA images were co-registered with the CT images using the stereotactic localizer box. Finally, the MRA study was digitally fused with the CT study using the automatic image fusion software of the radiosurgery planning system (BrainLAB AG). For the purpose of target delineation, the angiographic nidus was defined as the network of abnormal vessels between arterial feeder(s) and the pathologically early draining vein(s) [17].

Radiosurgery was performed using a 6-MV linear accelerator (Clinac 600 C, Varian Medical Systems Inc., Palo Alto, CA, USA) that was especially adapted for radiosurgery. Usually patients were treated with five noncoplanar arcs of 140° each, with identical beam weighting for all arcs, and a single circular collimator resulting in a typical spheroid dose distribution. After installation of the Novalis-shaped beam device (BrainLAB AG) in June 2002, only dynamic conformal arcs with dynamic multileaf collimators, producing a more conformal distribution of irradiation, were used. The dose was normalized to 100% and prescribed to the 80%-isodose line encompassing the bAVM. The clinically used prescription dose was dependent on the volume of the bAVM (normal tissue within 80%-isodose) with an 80% prescription dose of 21, 18, and 15 Gy for a volume of $\leqslant$7, 7–14, and $\geqslant$14 ml, respectively.

Follow-up consisted of an annual neurological examination and MR imaging of the brain, using the previously mentioned imaging protocol. Patients were followed annually with MRI until 3 years after radiosurgery, unless complete obliteration was diagnosed earlier. DSA was performed when MR imaging suggested complete obliteration. Alternatively, when MR imaging failed to show obliteration at 4 years after radiosurgery, DSA was performed to assess the need for repeat treatment. Angiographic obliteration of the bAVM was defined as the complete absence of abnormal vessels in the former nidus of the malformation, with disappearance or normalization of early draining veins from the area, and a normal circulation time on angiography [18,19].

Included in this study were all patients who underwent repeated radiosurgery of the same bAVM for the purpose of complete obliteration. Excluded from analysis were patients with a follow-up shorter than 2 years after the second radiosurgical procedure, except when angiographically confirmed complete obliteration or (re-)bleeding occurred earlier. The follow-up interval was considered complete when complete obliteration was reached, a (re-)bleeding occurred, or when new treatment, directed at bAVM obliteration, was initiated.

The patients' demographic data at the time of first (S1) and second (S2) radiosurgeries, and at last follow-up (FU) were reviewed retrospectively. Their clinical condition at S1, S2, and FU was classified according to the Modified Rankin Score (MRS). Pollock's modified bAVM-score, as well as the Spetzler–Martin gradation (SM) at S1 and S2 was determined [20,21]. A bAVM-related bleeding was defined as the sudden onset of neurological symptoms of decrease of consciousness with radiological confirmed presence of new hemorrhage in the surroundings of the bAVM.

MR images were independently reviewed by two experienced neuroradiologists (JB and RvdB) for the presence of complete obliteration, a new hemorrhage or radiological complications. The latter were graded as (1) no radiological abnormalities, (2) T2-hyperintensity, (3) T2-hyperintensity with cyst formation, or (4) necrosis [15]. The diagnosis of complete obliteration on DSA images was retrospectively reviewed.

Cumulative incidence of bAVM-related (re-)bleeding was calculated by dividing the number of bAVM-related hemorrhages after S1, and before obliteration by the number of people at risk in the cohort at S1. Time to obliteration was calculated using Kaplan–Meier curves. Statistical significance was determined using Student's T-test, χ^2-test, or log rank-test when this was appropriate. The results are reported as mean and 95% confidence interval (95% CI), unless otherwise stated. A two-tailed P-value <0.05 was chosen as the threshold for statistical significance. All statistics were performed using Statistical Package for Social Sciences v. 15.0 (SPSS Inc., Chicago, IL, USA).

Results

From a series of seventeen patients, fifteen, nine females and six males, were included in this study. Two patients were excluded from further analysis: one was lost to follow-up after he returned to his native country. In another the bAVM was contoured incompletely during the second radiosurgery planning in order to decrease the treatment dose on the optic nerve below 10 Gy.

Mean age at diagnosis of the bAVM was 31.3 years (95% CI: 23.1–39.5). There were eight left- and six right-sided bAVM; one bAVM was located in the vermis (Table 1). One patient was diagnosed with Hereditary Hemorrhagic Teleangietasias: three small

Table 1
Treatment parameters and Initial presentation of 15 bAVMs.

Patient	Location	Presentation[a]	Previous partial treatment[b]	S1				S2			
				Volume (ml)	SM[c]	bAVM-score[d]	Treatment-dose (cGy)	Volume (ml)	SM[c]	bAVM-score[d]	Treatment-dose (cGy)
1	Temporal	Headache	N/A	0.7	1	0.43	2100	2.0	1	0.66	2100
2	Temporal	Epilepsy	Endovascular embolisation (3)	2.8	1	0.90	2100	0.3	1	0.73	2100
3	Parietal	ICH	Resection	1.8	2	0.42	1800	4.0	2	0.72	1500
4	Cerebellum	FND	Endovascular embolisation (2)	14.1	1	2.13	1500	0.1	1	0.83	2100
5	Frontal	Epilepsy	Endovascular embolisation (2)	5.0	3	1.57	2100	9.4	3	2.08	1800
6	Occipital	ICH	N/A	4.2	3	1.38	1500	1.8	2	1.22	1500
7	Cerebellum	ICH	Endovascular embolisation (4)	8.7	4	1.47	1500	0.4	4	0.74	2100
8	Temporal	Screening	N/A	4.8	3	1.20	1800	4.2	2	1.22	2100
9	Cerebellum	ICH	Endovascular embolisation (1)	0.7	3	0.32	2100	4.8	1	0.84	1800
10	Temporal	Screening	N/A	0.6	1	0.92	2100	0.2	1	0.98	2100
11	Cerebellum	SAH	N/A	0.5	1	1.07	1500	0.5	1	1.15	2100
12	Temporal	Epilepsy	Endovascular embolisation (2)	6.4	4	1.00	1800	0.8	2	0.52	2100
13	Parietal	Screening	N/A	0.9	1	1.31	2100	1.2	1	1.44	2100
14	Basal ganglia	FND	N/A	12.2	4	2.34	1500	1.9	3	1.37	1500
15	Temporal	Epilepsy	Endovascular embolisation (2)	6.0	4	1.56	1420	0.2	3	1.08	2100

[a] ICH, intracranial hemorrhage; FND, focal neurological deficit; SAH, subarachnoid hemorrhage.
[b] The number between brackets refers to the number of embolisation sessions.
[c] SM: Spetzler–Martin grade [21].
[d] The bAVM-score refers to the modified score developed by Pollock and Flickinger [20] in order to predict the outcome after radiosurgery of bAVMs.