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Stereotactic "Functional Neurosurgery

# Combined Treatment Effects after Embolization and Radiosurgery in High-Grade Arteriovenous Malformations

**Case Report and Review of the Literature** 

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## **Key Words**

Multimodal therapy • Intracerebral arteriovenous malformation • Radiosurgery • Endovascular embolization • Microsurgery • Complications

#### Abstract

In recent years the multimodal therapy concept has been established for high-grade intracerebral arteriovenous malformations (AVM). One strategy of a multimodal treatment approach for patients with AVM (Spetzler grade V) is reported. After endovascular embolization, the patient underwent radiosurgical treatment of the remaining nidus with a linear accelerator, after which he developed a left-sided hemiparesis in conjunction with severe edema. Angiographic control 44 months after radiation showed an occlusion of the radiosurgically treated nidus. The remaining nidus could be removed by microsurgery. The combination of embolization and radiosurgery may provoke prolonged edema and permanent neurological deficits due to inflammatory perivascular changes.

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#### Introduction

Three therapy concepts are currently available in the treatment of intracerebral arteriovenous malformations (AVMs): microsurgical resection, endovascular embolization and radiosurgery use either separately or in combination. The combined application of all three types of treatment has recently been used in the treatment of Spetzler-Martin grade III–V AVMs. Although the results and complications of each process are well established, little is known about the results of the combination of all three methods. Only sparse reports are available about the course of the combined clinical treatment approach, particularly concerning the danger of a possible intensification of reactions caused by radiation and embolization.

In the following report a multimodal interdisciplinary treatment of an intracerebral AVM Spetzler grade V with a complicated clinical course will be presented.

## **Materials and Methods**

Embolizations were carried out via a transfemoral access with standard superselective catheter systems [1, 2]. Mostly n-butyl-2-cyanoacrylate is used as a tissue glue in combination with an oily contrast agent (lipiodol) [3].

Since 1991, a stereotactically modified linear accelerator is available for radiosurgery at the Eberhard-Karls University in Tübingen. A 6 MeV linear accelerator from Philips and the stereotactic system SRS 200 based on the Cosman-Robert-Wells stereotactic system is used. It is designed after the Gainesville system, optimizing the precision with the help of a stereotactic floorstand [4]. Precision of the collimator motion during gantry and table movement is controlled by two bearings, one for the isocentric accuracy of the collimator, the other for the rotation of the head of the floorstand. A gimbal-type bearing with a sliding collimator mount avoids any torque transfer from the LINAC head. The linear accelerator in combination with the floorstand and the CRW-stereotactic system has a precision of 0.3 mm [5]. The target volume in the treatment of AVMs is defined with the help of image fusion from angiogram, computer tomogram (CT) and magnetic resonance images (MRI). Depending on the localization and size of the AVM, the nidus dose ranges from 18 to 22 Gy.

### **Case Report**

A 43-year-old patient presented after a secondary generalized seizure. The patient had focal epilepsy attacks in the left half of the face and the left upper extremity for the prior 19 years. The occurrence of the attacks recently increased to an average of twice per month. At the time of admission the patient was clinically and neurologically unremarkable. MRI showed an extensive frontoparietal AVM (fig. 1). The size of the nidus was measured angiographically as  $6.1 \times 3.3 \times 4.1$  cm.

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**Fig. 1.** MRI scan showing the large right frontoparietal AVM before treatment.



**Fig. 2.** CT scan showing the perifocal edema after the last embolization, 10 months before radiosurgery.

Based on these findings, interdisciplinary multimodal therapy was chosen. First, five endovascular embolizations were carried out via a transfemoral access. As a result of the embolization, a reduction of the nidus of 25–30% could be obtained. After the last embolization, the patient suffered mild paresis of the left lower face. Otherwise the embolizations were tolerated well. CT scan after embolization showed the rest of the nidus as well as a perifocal edema (fig. 2).

The patient underwent radiosurgical treatment of the remaining nidus 10 months after the last embolization. After image fusion and three-dimensional planning, the patient underwent radiosurgical treatment involving seven arcs around one isocenter with a 32-mm collimator. The 90% isodose was 18 Gy, and the maximum dose was 20.54 Gy at the center of the target. Two peripheral nidus parts received only 80% of the isodose. The patient tolerated the stereotactic radiation with accompanying dexamethasone therapy very well.

Twelve months after irradiation, the patient developed an increasing distal paresis of the left upper extremity within a period of 6 weeks. An MRI showed a severe space-occupying right frontoparietal edema (fig. 3). Despite oral dexamethasone, further deterioration of the neurological status occurred with intensifying of the spastic paresis of the left upper extremity. In the further course of treatment, CT scans and MRI of the cranium showed a progressive degeneration of the pyramidal tracts on the right and slow decrease of the perifocal edema over a period of 13 months (fig. 4). The neurological symptoms remained. The control angiography 44 months after the irradiation showed a complete occlusion of the nidus encompassed by the 90% isodose. The part which was not included in the primary radiation field due to its size could still be identified. It showed a rapidly perfused remaining nidus in the area of the right frontoparietal operculum.

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**Fig. 3.** MRI scan showing severe edema 12 months after irradiation.

**Fig. 4.** MRI scan after the edema has resolved, showing the remaining nidus.

Therefore, a resection of the remaining nidus and partially obliterated blood vessels via a right frontoparietal osteoplastic craniotomy was carried out, with no complications. The symptoms which existed preoperatively remained stable. The postoperative angiogram showed complete elimination of the right frontoparietal AVM.

The neuropathological review of the resected tissue showed numerous small and large blood vessels with signs of chronic and partially necrotic inflamed infiltrate, especially in the are of the embolized vessels where an increase of foreign-body giant cells was noticed. Furthermore, numerous vessels could be found with shattered lamina elastica interna and media, with inceased collagenous fibers, separated by myofibroblasts as a morphological correlate of the radiation-induced changes.

Despite intensive physiotherapy the spastic hemiparesis of especially the left arm remained unchanged 6 years after irradiation.

#### Discussion

The indication for the treatment of intracerebral AVM is founded on the risk of morbidity and mortality caused by an intraparenchymal or subarachnoidal hemorrhage. The therapeutic aim is the complete elimination of the AVM and therefore the prevention of hemorrhage. The annual risk of hemorrhage of untreated AVMs varies between 1 and 4% with a mortality rate of 1% [6, 7] in 1 year.

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There are four different concepts of therapies for the treatment of AVMs available: (1) microsurgical resection, (2) endovascular embolization, (3) stereo-tactic radiosurgery and (4) the combined interdisciplinary use of these methods.

The total microsurgical resection of AVMs is regarded as a standard therapy [8, 9]. By using this therapy the risk of hemorrhage is immediately eliminated. Despite improved microsurgical techniques, there is a high surgical risk associated with AVMs in functionally important areas. The most important risk factors are localization, age, preoperative neurological state and size of the AVM [10]. Spetzler and Martin [11] developed a risk score based on the size, location and venous drainage. Low-grade AVMs (Spetzler grades I and II) should be directly treated operatively [9, 12].

The risk in extensive malformations limits operative success, but it can be improved by preoperative embolization [13]. The complete obliteration succeeds only in about 5-10% of the angiomas. If no further therapy follows a partial embolization, recanalization of the embolized angioma can occur [14]. This method can only be used as an unaccompanied therapy if the possibility of having a selective localization of the catheter of a single vessel or all the supplying vessels exists. In a partial reduction, a microsurgical resection or a radiological obliteration of the remaining nidus has to be undertaken.

The third option of therapy is stereotactic radiosurgery, which uses the effect of ionizing radiation on the endothelium of the vessels [15]. A specific disadvantage is the latent period which is needed for the complete obliteration of the malformation. AVMs with a nidus size below 3.5 cm which are difficult or not at all surgically accessible are most suitable for radiosurgical treatment [17].

For the treatment of widespread AVMs (Spetzler grades IV and V) situated in eloquent brain areas, the choice of stereotactic radiosurgery with microsurgical and/or endovascular procedures is the most effective treatment. This strategy of treatment is carried out over a period of several years [18].

In radiosurgery, however, the volume of the intracerebral AVM is an important variable regarding the occlusion and complication rates [19]. While the occlusion rate falls significantly below a dosage of 16–18 Gy, the complication rate clearly rises at a dosage above 25 Gy and a nidus size above 3.0 cm.

Because the dose-volume-tolerance relationship is crucial for the occurrence of complications and the chance of reducing the nidus size by endovascular embolization, the combination of embolization and radiosurgery is often most effective [20, 21].

In spite of the low dose that was chosen, the presented patient showed a severe and continuous perifocal edema due to disturbance of the blood-brain barrier with hemiparesis 12 months after irradiation (fig. 3). The MRI showed degeneration of the pyramidal tracts on the right-hand side.

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ownloaded by: ast Carolina University - Laupus Libr 50.216.68.200 - 3/9/2019 6:18:15 AN An edema which typically occurs 5–20 months after irradiation and resolves in the following 2–14 months is a well-known phenomenon in radiosurgery [22]. Subsequent complications due to radiation have been reported from all radiosurgical teams. The complication rate ranges between 2 and 5% [22–26]. Depending on the localization of the lesion, the edema may become symptomatic [27].

Brothers et al. [28] described in detail histopathological changes after endovascular embolization with Histoacryl in animal research over a period of 2 months. An acute and sometimes necrotic arteritis occurred, which developed into chronic granulomatous arteritis in the course of 1 month. There may also be intramural hemorrhage and necrosis, distortion of the lamina interna, extraction of the material used for embolization and recanalization.

Klara et al. [29] also observed in ten embolized AVMs inflammation changes in the area of the embolized vessels, which could be detected up to over 1 year after the embolization. Gruber et al. [30] described these inflammatory processes over a period of 4.5 years after the embolization.

The histopathological changes after radiosurgery are different from the inflammation changes after embolization, and are mainly characterized by endothelial proliferating reactions. Schneider et al. [31] showed that radiosurgical treatment leads to a change of the endothelium over a period of 1–3 years which induces a proliferation of muscles and also an increased collagen synthesis in the intima, which causes a progressive stenosis and an obliteration of the AVM treated radiosurgically. Similar results have also been reported by Chang et al. [32] and Szeifert et al. [33]. All changes caused by radiation appeared in a period of 1–3 years, after which no further pathological changes could be detected. This has also been reported by Steinberg et al. [23]. Doses below 20 Gy showed minor changes, whereas doses above 30 Gy caused major damage induced by the radio-surgery.

The neuropathological assessment in the previously reported case showed changes caused by radiosurgery with heavily fibrosed vascular walls, as well as chronic inflammatory changes in the area of the prior embolized vessels with foreign giant cell reactions. Regarding the long-lasting edema, as described in the case report, a summation of the inflammatory and vascular occluding effects might be responsible for the severe course.

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#### References

- Kerber C: Balloon catheter with calibrated leak: A new system for superselective angiography and occlusive catheter therapy. Radiology 1976;120:547–550.
- 2 Kerber CW, Heilman CB: New calibrated-leak microcatheters for cyanoacrylate embolization and chemotherapy. AJNR 1985;6:434–436.
- 3 Berenstein AB, Krall R, Choi IS: Embolization with n-butyl-cyanoacrylate in the management of CNS vascular lesions. AJNR 1989;10:883–887.
- 4 Friedman WA, Bova FJ: The University of Florida radiosurgery system. Surg Neurol 1989;32: 334–342.
- 5 Becker G, Major J, Christ G, Duffner F, Bamberg M: Stereotactic convergent beam irradiation: First experiences with the SRS 200 system. Strahlenther Onkol 1996;172:9–18.
- 6 Wilkins RH: Natural history of intracranial vascular malformations: A review. Neurosurgery 1985; 16:421–430.
- 7 Ondra SL, Troupp H, George ED: The natural history of symptomatic arteriovenous malformations of the brain: A 24-year follow-up assessment. J Neurosurg 1990;73:387–391.
- 8 Heros RC, Korosue K, Diebold PM: Surgical excision of cerebral arteriovenous malformations: Late results. Neurosurgery 1990;26:570–577.
- 9 Sisti MB, Kader A, Stein BM: Microsurgery for 67 intracranial arteriovenous malformations less than 3 cm in diameter. J Neurosurg 1993;79:653-660.
- 10 Frohwein RA, Stammler A, Kleinken B: Age as prognostic factor in arteriovenous angiomas and in intracranial aneurysms. Neurol Res 1984;6:54–56.
- 11 Spetzler RF, Martin NA: A proposed grading system for arteriovenous malformations. J Neurosurg 1986;65:476–483.
- 12 Drake CG: Cerebral malformations: Considerations for and experience with surgical treatment in 166 cases. Clin Neurosurg 1979;26:145–208.
- 13 Luessenhop AJ, Rosa L: Cerebral arteriovenous malformations: Indications for and results of surgery, and the role of intravascular techniques. J Neurosurg 1984;60:14–22.
- 14 Fournier D, Terbrugge KG, Willinsky R, Lasjaunias P, Montanera W: Endovascular treatment of intracerebral arteriovenous malformations: Experience in 49 cases. J Neurosurg 1991;75:228–233.
- 15 Colombo F, Benedetti A, Pozza F, Marchetti C, Chierego G: Linear accelerator radiosurgery of arteriovenous malformations. Neurosurgery 1989;24:833–840.
- 16 Steiner L, Linquist C, Adler JR, Torner JC, Alves W, Steiner M: Clinical outcome of radiosurgery for cerebral arteriovenous malformations. J Neurosurg 1992;77:1–8.
- 17 Becker G, Kortmann RD, Budach W, Buchgeister M, Duffner F, Grote EH, Bamberg M: High precision external radiotherapy of brain tumours. Onkologie 1998;21:290–297.
- 18 Steinberg GK, Chang SD, Levy RP, Marks MP, Frankel K, Marcellus M: Surgical resection of large incompletely treated intracranial arteriovenous malformations following stereotactic radiosurgery. J Neurosurg 1996;84:920–928.
- 19 Marks LB, Spencer DP: The influence of volume on the tolerance of the brain to radiosurgery. J Neurosurg 1991;75:177–180.
- 20 Friedman WA, Bova FJ, Mendenhall WM: Linear accelerator radiosurgery for arteriovenous malformations: The relationship of size and outcome. J Neurosurg 1995;82:180–189.
- 21 Ogilvy CS: Radiation therapy for arteriovenous malformations: A review. Neurosurgery 1990;26: 725–735.
- 22 Lundsford LD, Kondziolka D, Flickering JC, Bissonette DJ, Jungreis CA, Maitz AH, Horton JA, Coffey RJ: Stereotactic radiosurgery for arteriovenous malformation of the brain. J Neurosurg 1991;75:512–524.
- 23 Steinberg GK, Fabrikant JI, Marks MP: Stereotactic heavy-charged particle Bragg peak radiation for intracranial arteriovenous malformations. N Engl J Med 1990;323:96–101.
- 24 Colombo F, Pozza F, Chierego G, Casentini L, De Luca G, Francescon P: Linear accelerator radiosurgery for arteriovenous malformations: An update. Neurosurgery 1994;34:14–21.

Combined Treatment Effects in AVM

Stereotact Funct Neurosurg 2000;75:27–34

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- 25 Loeffler JS, Alexander E III, Siddon RL, Saunders WM, Coleman CN, Winston KR: Stereotactic radiosurgery for arteriovenous malformations using a standard linear accelerator. Int J Radiat Oncol Biol Phys 1989;17:673–677.
- 26 Souhami L, Olivier A, Podgorsak EB, Hazel J, Pla M, Tampieri D: Dynamic stereotactic radiosurgery in arteriovenous malformations: Preliminary treatment results. Cancer 1990;66:15–20.
- 27 Marks MP, Delapaz RL, Fabrikant JI, Frankel KA, Phillips MH, Levy RP, Enzmann DR: Intracranial vascular malformations: Imaging of charged-particle radiosurgery. Part II: Complications. Radiology 1988;168:457–462.
- 28 Brothers MF, Kaufmann JCE, Fox AJ, Deveikis JP: n-Butyl-2-cyanoacrylate substitute for IBCA in interventional neuroradiology: Histopathologic and polymerization time studies. AJNR 1989; 10:777–786.
- 29 Klara PM, George E, McDonnell DE, Pevsner PH: Morphological studies of human arteriovenous malformations. J Neurosurg 1985;63:421–425.
- 30 Gruber A, Mazal PR, Bavinzski G, Killer M, Budka H, Richling B: Repermeation of partially embolized cerebral arteriovenous malformations: A clinical, radiologic and histologic study. AJNR 1996;17:1323–1331.
- 31 Schneider BF, Eberhard DA, Steiner LE: Histopathology of arteriovenous malformations after gamma knife radiosurgery. J Neurosurg 1997;87:352–357.
- 32 Chang SD, Shuster DL, Steinberg GK, Levy RP, Frankel K: Stereotactic radiosurgery of arteriovenous malformations: Pathologic changes in resected tissue. Clin Neuropathol 1997;16:111–116.
- 33 Szeifert GT, Kemeny AA, Timperley WR, Forster DMC: The role of myofibroblasts in the obliteration of arteriovenous malformations after radiosurgery. Neurosurgery 1997;40:61–66.

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