Long-Term Outcome of Proton Beam Radiosurgery for Arteriovenous Malformations Larger Than 30 mm in Diameter

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Abstract

The effectiveness of proton beam (PB) radiosurgery for large lesions is greater than for other treatment modalities. At our institute, PB radiosurgery is used to treat arteriovenous malformations (AVMs). We report the outcome of PB radiosurgery for AVMs over a period of 15 years, focusing on the efficacy of PB radiosurgery combined with embolization for AVMs ≥ 30 mm in diameter. We retrospectively analyzed 11 patients with AVMs ≥ 30 mm in diameter who were treated with PB radiosurgery between June 1990 and September 2005 at the Proton Medical Research Center of the University of Tsukuba. The mean irradiation dose was 25.3 gray-equivalent, and the mean duration of clinical follow up was 134.2 months (median 138 months). Pre-radiosurgical embolization was performed in all cases. Complete obliteration was achieved in 9 of the 11 patients. One patient experienced post-radiosurgical hemorrhage, and 1 patient experienced radiation-related aggravation of clinical symptoms due to radiation necrosis. Eight patients had excellent outcomes. The multimodal therapy approach of combining pre-radiosurgical embolization and PB radiosurgery for AVMs yielded a favorable outcome for AVMs ≥ 30 mm in diameter. Thus, PB radiosurgery is a viable treatment option for AVMs ≥ 30 mm in diameter.

Key words: large arteriovenous malformation, proton beam radiosurgery, pre-radiosurgical embolization, long-term outcome, Bragg peak

Introduction

Arteriovenous malformations (AVMs) larger than 30 mm in diameter are thought to be associated with a low risk of hemorrhage and a high risk of treatment-related complications.^{6,10)} Therefore, most large AVMs are treated on a “wait-and-scan” basis. However, recent reports have indicated that patients with large AVMs have a higher rate of hemorrhage than previously reported.^{5,7,17)}

Gamma knife (GK) radiosurgery, which is usually adopted for small AVMs, is less effective for large lesions.³⁾ Charged particle beams used under stereotactic conditions offer the possibility of treating large AVMs with a low complication rate.¹⁸⁾ The pattern of energy distribution of the proton beams

(PBs) is characterized by an entrance region of a slowly rising dose, a rapid rise to the maximum dose (the Bragg peak), and a fall to near zero. Irradiation of larger targets is achieved by superimposing PBs of different energies, thereby generating a dose distribution that provides a moderate entrance dose, a uniform high dose within the target tissue, and a zero dose beyond the target.⁴⁾

Since 1990, we have been using PB radiosurgery for the treatment of patients with AVMs at the Proton Medical Research Center of the University of Tsukuba. Here, we present the outcome of PB radiosurgery for AVMs over a period of 15 years, focusing on the efficacy of PB radiosurgery combined with embolization for AVMs larger than 30 mm in diameter.

Materials and Methods

Thirty-one patients underwent PB radiosurgery between June 1990 and September 2005 at the Proton Medical Research Center of the University of Tsukuba. Twelve (38.7%) patients had AVMs ≥ 30 mm in diameter. One patient was lost to follow up. We retrospectively analyzed follow-up data of 11 patients with AVMs ≥ 30 mm in diameter. The following information for each patient was collected by review of medical records: age, sex, medical history, neurological examination results, and nidus size. The following tests were performed before the procedure: clinical neurological evaluation, cranial magnetic resonance (MR) imaging, cranial computed tomography (CT), and cerebral angiography. Nidus size was defined as the maximum diameter on MR imaging.

The 7 male and 4 female patients were aged from 11 to 46 years at initial presentation (mean 26.3 years). Eight patients reported previous hemorrhage, 1 presented with seizure, 1 had headache, and AVM was identified incidentally in 1. The total follow-up time was 1476 person-months. The mean duration of clinical follow up after PB surgery was 134.2 months. The mean nidus size was 40.0 mm. One patient was classified as Spetzler-Martin grade II, 4 as grade III, 5 as grade IV, and 1 as grade V. All patients underwent pre-radiosurgical embolization. All patients then underwent PB radiosurgery within 2 weeks of pre-radiosurgical embolization. None of the patients had received prior irradiation or radical surgical resection prior to radiosurgery. The mean irradiation dose was 25.3 gray-equivalent (GyE) at the center of the target volume (Table 1). GyE refers to the unit of energy absorbed by the human body or any material and accounts for the different biological effects exerted by various types of radiation. The relative biological effectiveness of the PB was assumed to be 1.1.¹¹⁾

The radiosurgical target was outlined by a radiation oncologist, and the target volume was defined by neuroradiologists and neurosurgeons in an interdisciplinary team approach. Prior to the radiosurgery, patients were fitted with a stereotactic frame (RADFRAME; Mizuho Co., Ltd., Tokyo) to enable precise positioning. Next, CT was performed using 5-mm or 3-mm thick sections for treatment planning with reference to the frame. The planned target volume was drawn on individual CT slices, taking into account all diagnostic information available, including cerebral angiography, MR imaging, and contrast CT findings. Drawing of the following critical structures was mandatory for each patient: the optic chiasm, hypothalamus, and brain stem. The

Table 1 Clinical characteristics in 11 patients with arteriovenous malformations

Age (yrs)	
mean $\pm$ SD	26.3 $\pm$ 13.6
range	11–46
Sex	
male	7 (63.6%)
female	4 (36.4%)
Follow-up period (mos)	
mean $\pm$ SD	134.2 $\pm$ 33.2
median	138
range	81–198
Symptom	
hemorrhage	8 (72.7%)
convulsion	1 (9.1%)
headache	1 (9.1%)
incident	1 (9.1%)
Nidus size (mm)	
mean $\pm$ SD	40.0 $\pm$ 9.2
range	30–60
Spetzler-Martin grade	
I	0 (0%)
II	1 (9.1%)
III	4 (36.4%)
IV	5 (45.5%)
V	1 (9.1%)
Dose (GyE)	
mean $\pm$ SD	25.3 $\pm$ 2.2
range	22.0–27.5

GyE: gray equivalent, SD: standard deviation.

maximum point doses permissible to the critical structures were 8 GyE for the optic chiasm and 16 GyE for the brain stem and hypothalamus. Multiple PBs converging on the target from different angles were developed to achieve a tight and conformal composite dose distribution. A minimum of 4 and a maximum of 6 different beam portals were used. The irradiation doses corresponding to a reference point in the center of the AVMs were calculated. An optimal composite isodose treatment plan was developed to cover most of the targeted AVMs with at least 80% of the reference dose and minimize exposure to the dose-limiting central nervous system structures. Custom-shaped collimators, tissue-equivalent boluses, and a variable-beam modulator were used to tailor each PB to the radiosurgical target and avoid critical normal structures (Fig. 1). This study was approved by the Institutional Ethics Committee at the University of Tsukuba.

Follow-up clinical examinations were performed at our hospital or elsewhere by referring physicians. Patients who did not visit a hospital were interviewed by telephone. Nidus obliteration was defined as disappearance of the nidus on angiography, and

Fig. 1 Case 8. Computed tomography scans showing the irradiation plan using 6 proton beam portals.

Table 2 Patient outcomes by Pollock et al.¹³⁾

	Nidus	Neurological examination
Excellent	complete obliteration	no new neurological deficit
Good	complete obliteration	new minor deficit
Fair	complete obliteration	new major neurological deficit
Unchanged	incomplete obliteration	no new neurological deficit
Poor	incomplete obliteration	any new neurological deficit
Dead		dead

as the disappearance of nidus enhancement and the absence of flow void signal abnormalities on MR imaging. Clinical outcomes were scored using the previously described classification, which ranges from excellent (complete obliteration and no new neurological deficit) to poor (incomplete obliteration and new neurological deficit) or dead (Table 2).¹³⁾

Continuous data are expressed as mean $\pm$ standard deviation. Discrete data are presented as counts and percentages. Correlation was assessed using the Pearson product-moment correlation coefficient. StatMate III for Windows (GraphPad Software, Inc., San Diego, California, USA) was used for all analyses. $P < 0.05$ was considered the threshold for significance.

Results

All patients underwent pre-radiosurgical embolization, which was aggressively performed in vessels if considered safe. Selection of the embolic materials was left to the discretion of the operator, and included N-butyl cyanoacrylate, a mixture of methyl and butyl methacrylate plus dimethylaminoethyl methacrylate copolymer (Eudragit-E; Evonik Röhm GmbH, Darmstadt, Germany), polyvinyl alcohol, and coils. Patients with multiple feeders underwent pre-radiosurgical embolization two or three times. None of the patients demonstrated complete obliteration following pre-radiosurgical embolization. One

Fig. 2 Kaplan-Meier curve showing the obliteration rates of arteriovenous malformations ≥ 30 mm in diameter.

patient experienced visual field impairment following embolization.

Cerebral angiography was performed in 10 patients after PB radiosurgery. Complete obliteration was achieved in 8 of the patients, and partial obliteration in 2, as assessed by cerebral angiography. One case was confirmed as complete obliteration on MR imaging. One patient with severe neurological deficits remained unchanged on MR imaging. The final results were complete obliteration in 9 (81.8%), partial obliteration in 1 (9.1%), and unchanged in 1 (9.1%). The mean time to complete obliteration was 58.8 months (range 24–144 months). The obliteration rates were 45.5% at 5 years, 63.6% at 7 years, and 75.8% at 10 years (Fig. 2). The time to complete obliteration was not significantly associated with nidus size or irradiation dose.

None of the patients underwent any additional treatment, such as surgical resection, embolization, or radiotherapy, after PB radiosurgery. One patient experienced post-radiosurgical hemorrhage (Case 9); she had a left cerebellar AVM 45 mm in diameter and suffered cerebellar hemorrhage. The lesion showed no change at 78 months after PB radiosurgery. Additional treatment was not performed because of severe neurological deficits. The patient died of rebleeding at 138 months after PB radiosurgery. The annual rebleeding rate was 0.8% per person-years. One patient experienced radiation-related aggravation of clinical symptoms (Case 3). Eight patients (72.7%) had excellent outcomes. Patient characteristics, treatment, and outcomes are shown in Table 3.

Discussion

Until recently, large AVMs were not aggressively treated, because of the high risk of treatment-related

Table 3 Summary of patients, treatments, and outcomes

Case No.	Age (yrs)/Sex	Symptom	Size (mm)	Spetzler-Martin grade	Dose (GyE)	Embolization	Nidus	Follow-up period (mos)	Outcome
1	11/M	hemorrhage	30	III	22.0	+	CO	99	excellent
2	36/M	hemorrhage	30	IV	27.5	+	CO	158	excellent
3	40/M	incident	31	IV	22.0	+	CO	115	fair (radiation necrosis)
4	23/F	hemorrhage	35	III	24.7	+	CO	127	excellent
5	16/M	convulsion	39	II	27.5	+	CO	144	excellent
6	21/M	hemorrhage	40	IV	27.5	+	PO	108	unchanged
7	46/F	hemorrhage	40	IV	24.2	+	CO	166	excellent
8	28/F	hemorrhage	40	IV	24.2	+	CO	198	excellent
9	11/F	hemorrhage	45	III	24.0	+	UC	138	death (rebleeding)
10	12/M	headache	50	III	27.5	+	CO	81	excellent
11	45/M	hemorrhage	60	V	27.5	+	CO	142	excellent

CO: complete obliteration, F: female, GyE: gray equivalent, M: male, PO: partial obliteration, UC: unchanged.

Table 4 Previous studies of the effects of irradiation on large arteriovenous malformations

Author (Year)	Radiosurgery method	No. of patients	Nidus size	Follow-up period	Pre-radiosurgical embolization (%)	Obliteration (%)	Complication (%)	Post-radiosurgical hemorrhage (%)
Pan et al. (2000) ¹²⁾	GK	48	> 15 ml	40 mos	0	25	3.9 (> 10 ml)	4.1
Silander et al. (2004) ¹⁵⁾	PB	14	> 10 ml	median 40 mos	0	14.3	0	0
Vernimmen et al. (2005) ¹⁸⁾	PB (HRST)	28	≥ 14 ml	median 62 mos	0	43	6	17.9
Sirin et al. (2006) ¹⁶⁾	GK (staged)	28	> 10 ml	median 50 mos	46	50	4	14
Bois et al. (2006) ²⁾	LINAC (HSRT)	15	> 10 ml	median 2.6 yrs	not described	20	6.7	20
Lee et al. (2009) ⁸⁾	GK	8	≥ 15 ml	mean 41.2 mos	13	25	not described	12.5
Present case	PB	11	≥ 3 cm	mean 134.2 mos	100	81.8	9.1	9.1

GK: gamma knife, LINAC: linear accelerator, HSRT: hypofractionated stereotactic radiotherapy, PB: proton beam.

complications. The annual pretreatment hemorrhage rate for all patients with high-grade AVMs (Spetzler-Martin grade IV or V) has been reported to be 10.4% per year, with rates of 13.9% and 7.3% per year in patients with and without hemorrhagic presentation, respectively.⁷⁾ Prospective follow up of 390 patients with AVMs revealed that the risk factors for hemorrhage from AVMs included deep-seated localization, large (>30 mm) nidus size, deep venous drainage, deep feeders, and the presence of a single draining vein or aneurysm.^{5,17)}

The American Heart Association does not recommend surgery for large lesions, those involving deep veins, or those with a Spetzler-Martin grade of IV or V.¹⁰⁾ Permanent occlusion of AVMs by embolization is achieved in only 10–30% of cases. Therefore, em-

bolization of AVMs is only one aspect of a multimodal approach to these lesions. Current indications for embolization can be divided into pre-surgical and pre-radiosurgical embolization in large AVMs.¹⁰⁾ Stereotactic radiosurgery has become an important treatment technique for the management of AVMs. Table 4 summarizes the findings of previous studies of radiosurgery. GK radiosurgery is indicated in small and deep lesions, but is not effective for AVMs larger than 30 mm.^{5,14,16)} Retrospective analysis of 400 patients with small AVMs (median 1.9 cm³) found that GK radiosurgery was most appropriate for patients with small AVMs, with complete obliteration rates of 72% at 3 years and 87.3% at 5 years.¹⁴⁾ In contrast, GK radiosurgery outcomes for large AVMs have generally been poor, obtaining

a complete obliteration rate of only 25% at 40 months in AVMs with volumes $>15\text{ cm}^3$, as compared to 77% for AVMs with volumes between $10\text{--}15\text{ cm}^3$.^{4,8,12} Volume-staged GK radiosurgery for large AVMs achieved a complete obliteration rate of 50%, with post-radiosurgical hemorrhage occurring in 14% of cases.¹⁶ The effectiveness of staged GK radiosurgery is thought to be limited, with no suitable treatment methods for relatively large and deep-seated lesions. Using linear accelerator-based (LINAC) radiosurgery, clinical outcomes for AVMs with volumes $>10\text{ cm}^3$ include low complete obliteration rate (13–20%) and high bleeding risk (20–23%).²

The pattern of energy distribution of the PBs in PB radiosurgery is characterized by an entrance region of a slowly rising dose, a rapid rise to the maximum dose (Bragg peak), and a fall to near zero. The sharp distal dose fall-off of the Bragg peak facilitates the use of range-modifying devices to tailor the distal edge of the high-dose region to the shape of the target volume. Bragg-peak ionization minimizes potential injury to adjacent vital structures, because of the focused peak of particle delivery at a predetermined depth.⁹ PBs for stereotactic irradiation of brain lesions with a complex shape or close to critical structures are therapeutically valuable.⁸ The obliteration rate will increase with accumulating PBs because of minimum injury being caused to adjacent structures. Study of a series of 5 patients with target volumes between 10 and 24 cm^3 found complete obliteration of AVMs in 2 patients and $>90\%$ reduction in 2 patients within 36 months, suggesting that PB radiosurgery is effective in large AVMs.¹⁵ Retrospective analysis of 28 patients with AVMs $>14\text{ cm}^3$ in volume found the rate of complete obliteration was 43%.¹⁸ Data from our institute showed the overall obliteration rate of AVMs $\geq 30\text{ mm}$ in diameter to be 81.8%. On the other hand, the obliteration rates at 5, 7, and 10 years were 45.5%, 63.6%, and 75.8%, respectively. PB radiosurgery demonstrated a long latent period from irradiation to obliteration, but was associated with a high complete obliteration rate. The long-term obliteration rate of GK and LINAC radiosurgery for large AVMs is unreported, but GK and LINAC radiosurgery for small AVMs had an effect at an early stage.^{14,19} PB radiosurgery makes the intima of the vessel uniformly hypertrophic, thus increasing the time course of obliteration of AVMs.

We suggest that pre-radiosurgical embolization contributed to our favorable outcomes. In our series, pre-radiosurgical embolization was performed in all patients with AVMs $\geq 30\text{ mm}$ in diameter. A previous patient with a ruptured brainstem AVM associ-

ated with a small pedicle aneurysm was treated successfully by endovascular embolization of the aneurysm followed by PB radiosurgery.⁹ However, our multimodal therapy approach combined pre-radiosurgical embolization and PB radiosurgery. The goal of pre-radiosurgical embolization is flow reduction in an attempt to minimize nidus. Recanalization occurred in about 15% of patients embolized and treated with GK radiosurgery.¹⁰ Recanalization of the embolized AVM compartments makes AVM delineation for radiosurgical planning more difficult.¹ On the other hand, the flow reduction achieved by pre-radiosurgical embolization can help to obliterate AVMs, because even AVMs with irregular shapes or $\geq 30\text{-mm}$ diameter can be uniformly irradiated through the use of PB radiosurgery.

Radiation-related complications of PB radiosurgery may occur after a long latent period, although PB radiosurgery allows minimization of irradiation injury to adjacent structures. In our series, 1 patient demonstrated radiation-related aggravation of clinical symptoms, namely, permanent motor deficits caused by radiation necrosis. The overall rate of radiation-related complications of GK and LINAC radiosurgery is 3.9–6.7%.^{2,12,16} However, the radiation-related complication rates of PB radiosurgery and that of GK and LINAC radiosurgery are difficult to compare because of the small number of cases reported, and the differences in the follow-up period. One patient died due to post-radiosurgical hemorrhage after 138 months. Although we believe that the rate of excellent outcomes was high (72.7%) for AVMs $\geq 30\text{ mm}$ in diameter, we suggest that the irradiation strategy for such cases should be further developed to reduce complications.

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