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Hypofractionated stereotactic radiotherapy for large arteriovenous malformations

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Abstract

Cerebral arteriovenous malformations (AVMs) are abnormal connections between the arteries and veins, with possible serious consequences of intracranial hemorrhage. The curative treatment for AVMs includes microsurgery and radiosurgery, sometimes with embolization as an adjunct. However, controversies exist with the treatment options available for large to giant AVMs. Hypofractionated stereotactic radiotherapy (HSRT) is one treatment option for such difficult lesions. We aim to review recent literature, looking at the treatment outcome of HSRT in terms of AVM obliteration rate and complications. The rate of AVM obliteration utilizing HSRT as a primary treatment was comparable with that of stereotactic radiosurgery (SRS). For those not totally obliterated, HSRT makes them smaller and turns some lesions manageable by single-dose SRS or microsurgery. Higher doses per fraction seemed to exhibit better response. However, patients receiving higher total dose may be at risk for higher rates of complications. Fractionated regimens of 7 Gy × 4 and 6–6.5 Gy × 5 may be accepted compromises between obliteration and complication. Embolization may not be beneficial prior to HSRT in terms of obliteration rate or the volume reduction. Future work should aim on a prospectively designed study for larger patient groups and long-term follow-up results.

Key Words: Arteriovenous malformation, hypofractionated stereotactic radiotherapy, radiosurgery

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INTRODUCTION

Cerebral arteriovenous malformations (AVMs) are congenital lesions in which abnormal collections of blood vessels composed of dilated arteries and draining veins with dysplastic vessels are present without interposed capillary beds and intervening neural parenchyma. The annual incidence is estimated at 1 person per 100,000[6,17] and prevalence at 18 per 100,000 population.[1,2] Hemorrhage rate is usually quoted to be 2–4% per year with a cumulative risk when left untreated.[5,10] The curative treatment for AVMs includes microsurgery and radiosurgery, sometimes with embolization as an adjunct.

The successful treatment of large AVMs remains a challenging task. No single treatment for large or giant AVMs can provide satisfactory results. Many of them were previously considered inoperable, especially those classified as Spetzler–Martin Grade IV or V.[30,31] Although

the optimal management is still controversial,[15,18] many clinicians now accept treatment of properly selected patients with large inoperable AVMs. However, treatment could lead to high mortality and morbidity. Experiences from a high-capacity medical center reported complete cure in only 36% of patients while adopting multimodality treatment for giant AVMs, at the cost of 15% mortality and another 15% long-term morbidity.[7]

Single-fraction stereotactic radiosurgery (SRS) has been proven effective in treating small AVMs, with complete obliteration rates of 72–96%.[18] Dose–volume relationship is unfavorable for large AVMs and the effective dosage might result in unacceptably high complication rates.[11,13,27] However, volume reduction was found even in AVMs that failed to completely obliterate,[19] making low-dose SRS with repeated treatments a viable option. Alternatively, large inoperable AVMs may be treated with radiosurgical techniques in dose or volume fractionation schemes to avoid damage to the surrounding tissue.[18]

Since the earliest attempt, fractionated stereotactic radiotherapy has been used in the treatment of large AVMs for over 20 years.[22,34] The obliteration rate was low after fractionated radiotherapy with a dose per fraction of 2–4 Gy to a total dose of up to 50 Gy and such treatment may cause significant side effects.[21] Therefore, the use of fractionated radiotherapy with lower doses per fraction cannot be recommended.

In contrast, fractionated stereotactic radiosurgery, also known as hypofractionated stereotactic radiotherapy (HSRT), usually involves delivering higher fraction dose to the target for up to 5 or 6 fractions. It can now be readily delivered by commercially available devices such as CyberKnife (Accuray Inc., Sunnyvale, CA, USA) and Novalis/Tx (BrainLAB AG, Feldkirchen, Germany; and Varian Medical Systems, Palo Alto, CA, USA). The objective of this article is to review recent literature for the treatment outcome of HSRT in terms of AVM obliteration rate and complication.

INDICATION AND PATIENT SELECTION

Unlike intracranial aneurysms, there is still no consensus in the definition of large or giant AVMs. The most widely accepted surgical grading system of AVM is the Spetzler–Martin classification,[30] where the size of the AVM is determined by the maximum diameter as small (<3 cm), medium (3–6 cm), or large (>6 cm). The last category was also known as "giant AVM" by some authors.[7,42] Unfortunately, this grading scale does not seem to correlate with successful AVM radiosurgery because it is insensitive to important factors such as AVM volume. Pollock and Flickinger proposed a radiosurgery-based scoring system,[28] which is calculated by AVM volume, patient age, and AVM location. Because they used continuous scale, there was no specified threshold for AVM volumes. Since a ball of 3 cm in diameter has an approximate volume of 14 mL, it is not uncommon to see 14 mL as a threshold for large AVMs in radiosurgical literatures.[26,35,39] However, there were many other definitions for large, extra-large, or giant AVMs.[3,4,9,27,37,41]

The major indication for HSRT, just like other alternative radiosurgical techniques, is *large inoperable* AVMs. As there is no consensus in definition, *large* AVMs refer to those too large to be effectively and safely treated with single-fraction SRS in this article. The term *inoperable* is also disputable. However, most authors preferred not to operate on AVMs of Spetzler–Martin Grade IIIB, IV, and V.[31]

Not all patients with large inoperable AVMs require aggressive treatment, including HSRT. On the contrary, treatment is not recommended for such patients with minimal or only mild symptoms. Accepted indications for treatment include repeated hemorrhage, progressive neurological deficits, intractable seizures, and other severe symptoms.[37]

TREATMENT DELIVERY

Radiobiologically, the linear-quadratic formulation is a model describing the cell survival curve. The α/β ratio is the dose where cell killing due to the linear and quadratic components are equal. Typically, the target cells for the obliteration of AVMs have a small α/β ratio in the dose–response curve, like late-responding normal tissues, so that fractionation is unfavorable for the obliteration of an AVM nidus. The real α/β ratios of AVMs, normal vessels, and normal neural structures are in fact not well known. Qi *et al*. reviewed HSRT literature and reported the α/β ratio of 2.2 ± 1.6 Gy.[29] While using the derived α/β ratio of 2.2 Gy, they proposed the fractionated regimens of 7.0 Gy × 4, 5.6 Gy × 6, 4.7 Gy × 8, and 4.2 Gy × 10.[29] The benefit of fractionation depends on the relative relationship between the AVM and the late-responding normal tissue in the irradiated area. As long as the α/β ratio for AVMs is larger than the surrounding brain tissue, fractionation schemes should, in principle, have therapeutic advantages over single-dose schemes.[4,29]

Generally, the fraction doses in the literature were within 4–7 Gy per fraction. Four to six fractions were delivered daily or every other day, making the whole course up to 2 weeks. The total doses usually ranged from 28 to 42 Gy. Some authors determined the dose according to the AVM volume and location, while others adjusted the dosage as the experience accumulated.[23,35] Since the AVM is a benign vascular lesion with a sharp border, the gross target volume (GTV) should be equal to the clinical target volume (CTV), i.e., the AVM nidus. However, dependent of the irradiation techniques, a margin of up

to 5 mm might be added to generate the planning target volume (PTV).[32]

Because the technical advancement in radiation delivery is very fast, we believe that, at the time being, most HSRT for AVMs are delivered by CyberKnife or Novalis/Tx systems. However, older techniques were utilized in most available literature. Newer techniques, such as RapidArc (Varian Medical Systems), are also being applied, but only short-term outcome is available.[32] Due to limited availability, as well as radiophysical and radiobiological differences, proton and heavy-particle treatments were excluded from our review.

OBLITERATION RATE

Single-fraction SRS has proved to be an effective method, especially in smaller AVMs. Several studies demonstrated both non-obliteration and complication rates rise when AVMs exceed 10 mL in size, with only a 32% obliteration rate after receiving single-dose SRS in one study of Gamma knife radiosurgery.[27] The two-year obliteration rate of AVMs larger than 4 mL is reported to be 40–58% in comparison to smaller AVMs, for which the obliteration rate is reported to be 85–100%.[14,24]

Comparison of the effects between SRS and HSRT showed no inferiority of AVM obliteration rate in the HSRT group. Aoyama and Chang used HSRT for patients with larger AVMs or AVMs at the eloquent area; even though the crude obliteration rate seemed lower in the HSRT group, statistical analysis did not reveal significant difference [Table 1]. The effectiveness of HSRT may be underestimated by the selection bias.[4,8]

Regardless of the total irradiation dose given, there seems to be a minimal dose per fraction required to obtain the desired high obliteration rates. A 7.2-fold greater obliteration rate of 7-Gy over 5-Gy cohorts was reported by Veznedaroglu *et al*.,[35] and other studies also reported obliteration rate of 50–83% for doses of 7 Gy versus 8–22% for doses less than 7 Gy.[4,8,23] The difference between the 7-Gy and ≥7-Gy groups was not statistically significant.[18] For lower doses tested, Xiao *et al*. reported that 6-Gy group showed better response rate than 5-Gy group.[37]

A pooled analysis of previous reports has shown the HSRT of 7-Gy fraction to be superior with a AVM obliteration rate of 65% compared to 38.5% of single treatment, 25% of volume fractionation, and 58% of salvage treatment.[18]

For smaller AVMs, several studies have suggested that embolization is a negative predictor of obliteration.[16,25,40] However, reduction of size by embolization increased the obliteration rate in large AVMs as reported by Veznedaroglu *et al*.[35] The benefit was not observed by another report.[37] The tendency of suboptimal response of embolized AVMs might be caused by more difficult target definition and subsequent volumetry due to image artifacts caused by embolization materials. It is also possible that AVMs undergoing embolization are simply more complicated AVMs accompanied by fistulae and aneurysms, making them worse responders. In general, the use of routine pre-HSRT embolization is questionable due to the lack of solid evidence of benefit in different studies. Embolization may be reserved for AVMs associated with aneurysms or large arteriovenous fistulae.

COMPLICATIONS

Eliminating the risk of hemorrhage in patients with AVMs through obliteration is the primary goal of therapy. Latency period between irradiation and eventual obliteration is cited as the chief disadvantage when compared to microsurgery. There was a decrease in the incidence of hemorrhage as compared to the natural course according to one report.[20] However, several confounding variables in the literature make it difficult to determine the real hemorrhage rate following irradiation, especially when patients presented with rupture prior to the treatment, or received embolization, surgery, previous radiosurgery while entering the studies. Several of the reports also failed to report the risk of bleeding in person-year expression, making it difficult to compare the differences across the studies. Comparing the annual bleeding risk of AVMs after HSRT and SRS, the reported figure of 3–9% in the HSRT group seems slightly higher than most SRS series. However, the comparison might be an invalid one because HSRT is usually reserved for larger AVMs or AVMs in the eloquent area in these studies.[29,37]

Radiation-related adverse effects also constituted another category of commonly seen complications after HSRT. Transient symptoms are usually associated with increased signal change on T2-weight magnetic resonance image, while radiation necrosis or cyst formation may also develop.[12,33,38] HSRT does not cause increased incidence of T2 signal change, which typically produces clinically silent or mild symptoms, and is usually transient.[4] Radiation necrosis, in contrast, is the most serious type of late radiation change. The rates of radiation necrosis in patients treated with radiosurgery are usually quoted to range from 3 to 7%.[12,23,33] A high total dose of HSRT does not seem to correlate well with obliteration, but may be more responsible for a higher rate of complications. Veznedaroglu *et al*. reported relatively high adverse effects (86% radiographic, 28% symptomatic) with 7-Gy fraction for a total dose of 42 Gy. Among these were one patient with venous infarction outside the 10% isodose prescription line, which developed 10 months after receiving HSRT, and the patient subsequently remained vegetative.[35] Other studies in which 28–35 Gy was used

Table 1: Studies of hypofractionated stereotactic radiotherapy series

Study	No.	Size/volume	Total dose/ fractions	Prior treatment	Follow-up time	Obliteration rate	Complication
Aoyama, 2001[4]	HSRT: 26	Eloquent area or >2.5 cm, mean: 2.26 cm	24–28.8 Gy/4 (mean: 26.8 Gy)	Embolization: 11% Surgery: 9%	>1 year (mean: 35.4 months)	At 3 years: 53%	Hemorrhage: 12% Radiation necrosis: 0%
	SRS: 27	Non-eloquent area or <2.5 cm, mean: 1.78 cm	12–20 Gy (mean: 18.5 Gy)		>1 year (mean: 34.6 months)	At 3 years: 71%	Hemorrhage: 7% Radiation necrosis: 8%
Lindvall, 2003[23]	HSRT: 29	Mean: 11.5 mL	30–35 Gy/5 (median: 32.6 Gy)	Embolization: 38% Surgery: 17%	8 years (mean: 38 months)	At 2 years: 56% (4–10 mL) 50% (>10 mL) At 5 years: 81% (4–10 mL) 70% (>10 mL)	Hemorrhage: 7% Epilepsy: 7% Radiation necrosis: 7%
Veznedaroglu, 2004[35]	HSRT: 24	Mean: 23.8 mL	42 Gy/6 (6 patients)	Embolization: 86%	>5 years (mean: 102 months)	83% (at mean latency 108 ± 52 weeks)	14% (86% with radiographic change)
		Mean: 14.5 mL	30 Gy/6 (18 patients)	Embolization: 57%	>5 years (mean: 82 months	22% (at mean latency 192 weeks)	8.7% (30% with radiographic change)
Chang*, 2004[8]	HSRT: 33	Eloquent area or >2.5 cm	20–28 Gy/4 (mean: 25.9 Gy)	Embolization: 10% Surgery: 15%	Mean: 52 months	At 3 years: 32% At 5 years: 61% At 6 years: 71%	Hemorrhage: 22%/5 years Radiation necrosis: 3%
	SRS: 42	Non-eloquent area or <2.5 cm	12–20 Gy (mean: 19.3 Gy)			At 3 years: 52% At 5 years: 81% At 6 years: 81%	Hemorrhage: 8%/5 years Radiation necrosis: 10% Epilepsy: 2%
Zabel-du Bois, 2006[41]	HSRT: 15	> 4cm Median: 27 mL	20–32.5 Gy/4–5 (median: 26 Gy)	Embolization: 27% Surgery: 0%	Median: 2.6 years	At 3 years: 17% At 4 years: 33%	Hemorrhage: 20% Radiation necrosis: 0%
	SRS: 33	Median: 7 mL	15–19 Gy (median: 17 Gy)	Embolization: 24% Surgery: 3%		At 3 years: 47% At 4 years: 60%	Hemorrhage: 21% Radiation necrosis: 0%
Xiao, 2010[37]	HSRT: 20	>5 cm, median: 46.84 mL	25–30 Gy/5–6 (median: 30 Gy)	Embolization: 50%	Median: 32 months	0% Median post-treatment volume: 13.51 mL	Increase seizure: 5% Ischemic stroke: 5% Hemorrhage: 2.06%/year

*Continuum of the Aoyama *et al.* study, HSRT: Hypofractionated stereotactic radiotherapy

have reported low rates of radiological changes and mild symptoms despite the same per fraction doses.[4,8,23]

STAGED TREATMENT

While other reports compared the effects of HSRT with SRS for large AVMs, Xiao *et al.* viewed HSRT as a first stage of the multimodality treatment for large inoperable AVMs.[37] They followed Wowra *et al.*,[36] analyzing the obliteration dynamics of AVMs after irradiation. The time-dependent regression of transnidal flow after irradiation, or obliteration dynamics, is a determinant of the latency period. Xiao *et al.* also measured the volume changes and fit the numbers into the exponential decay model.[37] After HSRT, large inoperable AVMs decreased 44% in volume annually. Therefore, HSRT turns some of these AVMs into manageable lesions, which could then be treated by single-dose SRS or microsurgery.[37] Although this approach seems to be reasonable for really large lesion, it apparently prolongs the latency period and additional bleeding during this period can be expected.

CONCLUSION

The rate of AVM obliteration utilizing HSRT as a primary treatment was comparable with that of SRS. For

those not totally obliterated, HSRT makes them smaller and turns some lesions manageable by single-dose SRS or microsurgery. Higher doses per fraction seemed to exhibit better response. However, patients receiving higher total dose may be risked for higher rate of complication. Fractionated regimens of 7 Gy × 4 and 6–6.5 Gy × 5 may be accepted compromises between obliteration and complication. Prior embolization may not be beneficial prior to HSRT in terms of obliteration rate or the volume reduction. Future work should focus on a prospectively designed study, for larger patient groups and long-term follow-up results.[16]

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