Advances in the radiosurgical treatment of large inoperable arteriovenous malformations

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Radiosurgery has proven useful in the treatment of small arteriovenous malformations (AVMs) of the brain. However, the volume of healthy tissue irradiated around large lesions is rather significant, necessitating reduced radiation doses to avoid complications. As a consequence, this can produce poorer obliteration rates. Several strategies have been developed in the past decade to circumvent dose-volume problems with large AVMs, including repeated treatments as well as dose, and volume fractionation schemes. Although success on par with that achieved in lesions smaller than 3 ml remains elusive, improvements over the obliteration rate, the complication rate or both have been reported after conventional single-dose stereotactic radiosurgery (SRS). Radiosurgery with a marginal dose or peripheral dose < 15 Gy rarely obliterates AVMs, yet most lesions diminish in size posttreatment. Higher doses may then be reapplied to any residual nidi after an appropriate follow-up period. Volume fractionation divides AVMs into smaller segments to be treated on separate occasions. Doses > 15 Gy irradiate target volumes of only 5–15 ml, thereby minimizing the radiation delivered to the surrounding brain tissue. Fewer adverse radiological effects with the use of fractionated radiosurgery over standard radiosurgery have been reported. Advances in AVM localization, dose delivery, and dosimetry have revived interest in hypofractionated SRS. Investigators dispensing ≥ 7 Gy per fraction minimum doses have achieved occlusion with an acceptable number of complications in 53–70% of patients. The extended latency period between treatment and occlusion, about 5 years for emerging techniques (such as salvage, staged volume, and hypofractionated radiotherapy), exposes the patient to the risk of hemorrhage during that period. Nevertheless, improvements in dose planning and target delineation will continue to improve the prognosis in patients harboring inoperable AVMs. (DOI: 10.3171/FOC-07/12/E7)

KEY WORDS • arteriovenous malformation • hemorrhage • stereotactic radiosurgery

Since the first GK unit was introduced ~ 4 decades ago, GKS has been an important noninvasive means of treating various lesions of the brain. A GK unit uses 201 60Co sources, initially of 30 Ci each or a total of about 6000 Ci. Thus far, over 300,000 patients have been treated with GK worldwide, and the AVM has been 1 of the 4 major brain pathological entities treated among these patients. Arteriovenous malformations are congenital, nonneoplastic groupings of mature vessels in which blood is shunted from feeding arteries to the draining veins at a central nidus. Arteriovenous malformations can occur throughout the body; in the brain they commonly arise supratentorially in the distribution of the middle cerebral artery.2 The incidence is estimated at 1 person per 100,0003,22 and prevalence at 18 per 100,000.1 Despite their rarity, AVMs represent clinically important entities. Hemorrhage is the most frequent presentation,4,6 including intracerebral (41%), subarachnoid (24%), intraventricular (12%) locations, and various combinations (23%). In addition, these lesions can cause epilepsy, headache, and focal neurological deficits. Most are clinically silent at the initial diagnosis, however.

Little is known about large AVMs. Characterization, from relative hemorrhage rates to the propensity to cause seizures, has met with controversy.20,30,41 One feature unanimously agreed on, however, is their irregular response to conventional SRS.

Salvage Therapy

Stereotactic radiosurgery has proven effective in treating small (≤ 3 ml) AVMs, with complete occlusion rates reported at 72–96%.8,19,47 However, less impressive results have been encountered with progressively larger lesions.7,20,26,33,35,46,47 Several studies demonstrated that both nonobliteration and complication rates rise when AVMs exceed 10 ml in size. Pan et al.6 found that only 24 (32%) of 76 patients with large AVMs (≥ 10 ml) were cured with

Abbreviations used in this paper: AVM = arteriovenous malformation; GK = Gamma Knife; GKS = GK surgery; HSRT = hypofractionated stereotactic radiotherapy; MR = magnetic resonance; SRS = stereotactic radiosurgery; ST = salvage therapy; SVR = staged volume radiosurgery.
single-dose SRS. When treatment of large lesions was compared to that of smaller lesions, patients suffered more adverse radiological effects, including permanent neurological deficits. It was previously thought that volume was an independent factor in AVM occlusion. However, multivariate regression of dose–response curves for AVMs has shown that only the minimum dose is significant. The results reported by Pan and associates and in similar studies have led many investigators to conclude that the dose–volume relationship is unfavorable for large AVMs, and results in unacceptably high complication rates.

In an effort to circumvent dose–volume limitations some authors have used suboptimal doses of radiation (<15 Gy) and simply retreated lesions that failed to obliterate. Longitudinal data from SRS treatment sites show a general reduction in AVM volume even in lesions that fail to completely occlude. Salvage therapy presupposes that a second irradiation may induce or hasten AVM obliteration in already reduced nidi due to higher tolerated dose and more accurate delineation. Although no authors have focused on large AVMs specifically, the existing literature suggests that ST may become a viable option in their treatment.

One early study demonstrated that the obliteration rate after ST was equivalent to that predicted by the K index (nidus volume $\times$ D$_{MAX}$) for initial treatment. Apparently, small and diminished AVMs respond similarly to radiation, alleviating concern of radioresistance in the latter. Recently, investigators reported on 52 patients treated with ST, 34 of whom presented with AVMs $>$ 10 ml. After the first treatment with SRS, 29 lesions were reduced to $<$ 10 ml in size, placing them in a cohort with 63% obliteration rate at 36 months after ST. However, the manner in which the data are presented precludes determination of how many of the original lesions $>$ 10 ml were actually cured. Despite repeated exposure, patients tolerated ST well; only 2 of 46 (5 of the original 52 were lost to follow-up and 1 died of AVM rupture) suffered adverse radiological effects, 1 permanent and the other transient. The complication rate associated with ST is comparable to that after primary SRS, but it is acknowledged that patients incur a cumulative risk after ST. By aiming to reduce AVM volume at first, rather than achieving outright obliteration, ST avoids both the dose–response and dose–volume problems in the treatment of larger lesions. However, the paucity of data on how large AVMs respond to ST renders the advantage tentative.

**Staged Volume Radiosurgery**

In SVR the AVM is divided into 2 or more volumes radiographically, and each is treated on a separate occasion. The strategy aims to reduce the non-AVM 12-Gy volume while still delivering a minimum dose $\geq$ 15 Gy at the 50% isodose line to each volume to be treated. Typically, hemispheric lesions are irradiated in 10–15 ml volumes, compared to 5 ml volumes for deep brain regions where the use of 12 Gy is associated with greater complications. By treating 1 segment per stage, the surrounding brain tissue is given time to repair radiation-induced injury. Representative imaging studies obtained prior to each stage of 3-stage GKS in a 31-year-old woman are shown in Figs. 1 and 2. This patient was treated at Northwestern Memorial Hospital. To date, only 1 group has published results from several patients treated with SVR that included a significant follow-up period. The study describes 7 (25%) of 28 patients who were cured with SVR and an additional 4 in whom the nidus was nearly obliterated after 36 months’ follow-up. The median pretreatment AVM volume was 24.9 ml. Despite only comparable occlusion rates to single-dose radiosurgery, SVR does appear safe with acceptable complication rates. SVR has been shown to reduce the non-AVM 12 Gy volume by 27%. Less brain exposure may be responsible for the transient adverse radiological effects in only 4 (14%) of 28 patients, including 1 patient who was treated with SVR twice. This is in contrast to the findings of Miyawaki and colleagues who reported a 27% complication rate, including permanent neurological deficits and death, in treating lesions $\geq$ 14 ml with single-dose SRS.

The evolving role of SVR in the management of large AVMs is fully illustrated in a recent case report in which the use of staged volume aided in the ultimate reduction of the AVM. The authors of the study describe how a previously inoperable AVM was not only reduced but also thrombosed by SVR, thereby facilitating its excision. Further trials are necessary to optimize variables such as...
minimum dose, time between stages, and volume per segment. In addition, given the large AVM size in the present study, it will be interesting to examine 5- and 7-year obliteration rates.

Hypofractionated Stereotactic Radiotherapy

Hypofractionated stereotactic radiotherapy has been used in the treatment of large AVMs for over 20 years. Fractionated daily doses of 2–7 Gy are delivered over several days using a linear accelerator and stereotactic head frame. The total HSRT dose exceeds what can be safely administered in a single radiosurgical treatment. Hypofractionated stereotactic radiotherapy may also exploit an AVM’s early radiation response compared with normal brain tissue. Late responding tissue with a low α/β ratio would suffer more gradual injury, and would thus be easier to repair. Early studies of HSRT were performed without stereotactic MR imaging and MR angiography, liquid adhesive embolization, or conformal dose planning. Newer technology has provided more accurate AVM localization and dose delivery, yielding higher obliteration rates and fewer complications. Differences in reporting time to follow-up, lesion size, hemorrhage rate, and method of occlusion verification among the various studies make comparison difficult. However, important trends have emerged.

Regardless of total dose, there appears to be a minimum dose per fraction necessary to achieve high occlusion rates. One group reported a 7.2-fold greater occlusion rate of 7-Gy over 5-Gy cohorts. Investigators using per fraction doses < 7 Gy reported occlusion rates of 8–22%, compared with 50–83% for doses of 7 Gy or greater. The AVMs described in these studies were all large, and occlusion was verified after 5 years of follow-up in those using doses less than 7 Gy and after 3–5 years in those using doses of 7 Gy or more. The total radiation dose ranged from 30 to 50 Gy, and the difference between the < 7-Gy and ≥ 7-Gy groups was not statistically significant.

A high total dose does not correlate with occlusion, but
may be responsible for a higher rate of complications. In a group of 7 patients treated with 42 Gy, 6 (86%) developed T2-weighted changes on MR imaging. One patient suffered a venous infarction and was subsequently determined to be in a vegetative state. In contrast, the authors of other studies in which 32–35 Gy was used have reported low rates of radiological changes and mild symptoms despite equivalent per fraction doses.

The gradual effects of radiotherapy in general are especially pronounced in large AVMs. Hypofractionated stereotactic radiotherapy continues to obliterate large lesions well beyond 24 months’ follow-up. Declaring treatment failure before 5 years seems premature given significant occlusion rates (20–27%) between 2 and 5 years after treatment. Nevertheless, one must balance the risk of retreatment complications against the risk of hemorrhage during AVM patency. Determining the true α/β ratio may allow researchers to better exploit the differences between AVM and normal brain tissues, resulting in shorter latency periods.

### Risk of Hemorrhage

Eliminating the risk of hemorrhage in patients with AVMs through obliteration is the primary goal of SRS. Latency between SRS and eventual obliteration is cited as a chief disadvantage of this method compared with surgical excision, but what effect (if any) SRS has on the intermittent hemorrhage rate remains controversial. Unfortunately, several confounding variables in the literature make it difficult to compare hemorrhage rates in included patients with the natural history of AVMs. For example, many patients present with rupture prior to treatment and thus carry an increased risk of another hemorrhage over the next 2 years. Also, many studies combine embolization, retreatment with SRS, and attempted surgery in their analysis of the risk of hemorrhage after SRS. Generally small populations and short follow-up times factor in as well. Among investigators reporting on modified SRS techniques such as SVR and hypofractionated SRS, few have classified the hemorrhage rate in person-years. It appears, at least from median or mean follow-up time and percentages of patients who experienced hemorrhages, that SRS hemorrhage rates are in line with the natural history rate of 2–4% per year. This finding agrees with larger studies examining the risk of AVM hemorrhage after radiosurgery. The comparison of the results of SRS techniques are summarized in Table 1.

### Conclusions

Much progress has been made toward safe yet efficacious dose delivery in the treatment of large AVMs. However, these lesions still pose a formidable challenge to neurosurgeons. Hypofractionated stereotactic radiotherapy has benefited from years of research on dosimetry and targeting, but newer techniques may well prove useful to future clinicians. Advances in understanding of the radiobiology, optimal dose selection, and refinements in techniques to minimize adverse events will all contribute to make these formidable vascular malformations routinely curable.

### Disclaimer

No funding was provided by Leksell, General Electric, Northwestern Memorial Hospital, or any other entity. The authors have no financial ties to Elekta or the maker of any other radiosurgery devices.

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Accepted October 17, 2007.
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