

# Multimodal Treatment Strategy for Spetzler–Martin Grade III Arteriovenous Malformations of the Brain

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## Abstract

The Spetzler–Martin (S–M) grading scale was developed to assess the risk of postoperative neurological complications after the surgical treatment of arteriovenous malformations (AVMs) of the brain. Treatment-associated morbidity and poor outcomes are particularly relevant to Grade III AVMs and improving the safety while attaining acceptable cure rates still poses a challenge. A multimodal treatment strategy combining surgery, embolization, and radiosurgery is recommended for S–M Grade III AVMs because of the surgical risk. Grade III AVMs are the heterogeneous group that has been further divided into subgroups according to the size, the location in eloquent cortex, and the presence of deep venous drainage. The risks associated with different treatment modalities vary depending on the subgroup, and the rating scales have been further refined to predict the risk more accurately and help determine the most appropriate treatment choice. Previous results for the treatment of S–M Grade III AVMs vary widely among studies, and the treatment modalities are also different in each study. Being familiar with previous treatment results is essential for improving treatment outcomes.

Key words: arteriovenous malformations, embolization, multimodal treatment, radiosurgery, Spetzler–Martin grading

## Introduction

In patients with unruptured arteriovenous malformations (AVMs) of the brain, studies such as a Randomized trial of Unruptured Brain AVMs (ARUBA)<sup>1)</sup> and The Scottish Intracranial Vascular Malformation Study (SIVMS; a population-based inception cohort study)<sup>2)</sup> have shown that conservative medical management is superior to interventional therapy for achieving better outcomes. However, the design and conclusions of the ARUBA and SIVMS studies may not reflect recent technical advancements, especially in surgical techniques and the use of new endovascular devices.

The Spetzler–Martin (S–M) grading scale<sup>3)</sup> for surgically excised AVMs has demonstrated a correlation with the incidence of postoperative neurological complications, and is widely accepted. For S–M Grade III AVMs, a combined multimodal treatment strategy with surgery, embolization, and radiosurgery is recommended because of the surgical risk.<sup>4,5)</sup>

Unlike low-grade AVMs (S–M Grade I and II) that are associated with lower surgical risk,<sup>3,4,6,7)</sup> treatment-associated morbidity and poor outcomes

become important problems for Grade III AVMs. Previous results for the treatment of S–M Grade III AVMs vary widely among studies, and the treatment modalities were also different in each study. Treating S–M Grade III AVMs safely with acceptable cure rates poses important and challenging problems. It is necessary to be familiar with previous treatment results in order to improve treatment outcomes. With technological advances in treatment, especially the introduction of Onyx (eV3, Irvine, CA), multimodal treatment strategies have changed significantly. In this study, we have presented the previous treatment outcomes for S–M Grade III AVMs, and discussed multimodal treatment strategies that would avoid surgical complications and achieve greater efficacy and cure.

## S–M Grade III AVMs

The risk of hemorrhage for unruptured brain AVMs is approximately 2.2% per year.<sup>8)</sup> In the ARUBA study, a similar rate of spontaneous hemorrhage was also reported.<sup>1)</sup> Pandey et al. reported that the hemorrhage rate for Grade III AVMs was 2.1/patient/year.<sup>9)</sup> It does not differ significantly from the hemorrhage rate for all types of AVMs.<sup>1,8)</sup> However,

the detailed natural history and outcome for S–M Grade III AVMs has not been reported separately.

According to the AHA Scientific Statement, a combined approach with embolization followed by surgery is often feasible for S–M Grade III AVMs.<sup>5)</sup> The importance of a multimodal treatment strategy has been recognized, and this approach is expected to reduce the morbidity and improve the outcomes. However, S–M Grade III AVMs constitute a heterogeneous group that has four subtypes: S1E1V1, S2E0V1, S2E1V0, and S3E0V0. Despite these subtypes having the same S–M Grade, several studies have demonstrated that each subtype of Grade III AVMs has different therapeutic outcomes. Many authors have suggested that the S–M grading scale should be modified to emphasize the surgical risk of Grade III AVMs and that it may not be appropriate to categorize the four subtypes of S–M Grade III together as one Grade.<sup>4,9-11)</sup>

S–M Grade III AVMs were first divided into two types by de Oliveira et al.<sup>12)</sup>: Grade IIIA (large size) and Grade IIIB (small, in eloquent areas), but the definition of the AVM size was unclear. The authors recommended preoperative embolization followed by microsurgical resection for Grade IIIA and radiosurgery for Grade IIIB. Spetzler and Ponce<sup>4)</sup> modified the five-tier classification (the S–M grading scale) to Spetzler–Ponce grading (a three-tier classification), in which Class A combines S–M Grades I and II, Class B represents S–M Grade III AVMs, and Class C combines S–M Grades IV and V. The proposed three-tier classification of AVMs would provide a guide for deciding the treatment strategy and predicting the outcome. The management of Class B AVMs is more individualized and typically requires a multimodal approach. These nuances reflect the complexity and heterogeneity of S–M Grade III AVMs. Davidson and Morgan<sup>13)</sup> then examined the risk of adverse outcomes for microsurgery. They modified the S–M grading scale by dividing Grades I and II, and Grades II and IV into non-eloquent cortex, and Grades III to V into eloquent cortex, and calculated the surgical risk as 0.7%, 17%, and 21%, respectively. Pandey et al.<sup>9)</sup> reported high obliteration rates with multimodality management of S–M Grade III AVMs. They proposed that S–M Grade III AVMs should be classified into Grade III (small: <3 cm) and III (large: ≥3 cm) because the AVM size plays a major role in predicting new neurological deficits. Andrade-Souza et al.<sup>14)</sup> reported the radiosurgical results of S–M Grade III AVMs classified by the radiosurgery-based AVM score (RBAS)<sup>15)</sup> and modified S–M Grade III to Grade IIIA (>3 cm) and IIIB (<3 cm).

## Surgical Resection of S–M Grade III AVMs

The S–M grading scale<sup>3)</sup> is associated with the incidence of postsurgical neurological complications, and complication rates increase as the Grade increases. In Spetzler's surgical series, the morbidity (for minor and major deficits) and mortality rates were 16% and 0% for S–M Grade III AVMs.<sup>3)</sup> Heros et al.<sup>16)</sup> reported the outcome of surgical excision for Grade III AVMs. The early complication rate (including transient) was 31.8%, and the late complication rate (permanent neurological deficit) was 11.4%. Onyx became available recently and many reports of surgical results include embolization. Thus, evaluating the risk of surgery performed as a single modality may be difficult.

In a systematic review and meta-analysis, the morbidity leading to permanent neurological deficits or death occurred in a median 7.4% of patients (range, 0–40%) after microsurgery for all grades of AVMs.<sup>17)</sup> The meta-analysis revealed that the surgical morbidity rate for Grade III AVMs seemed to be higher than that of AVMs overall. In comparison with low-grade AVMs, patients with S–M Grade III AVMs came to be known as a high-risk surgical treatment group. Therefore, a multimodal strategy combining surgery with embolization is considered to improve the outcome.

## Endovascular Embolization for S–M Grade III AVMs

In a systematic review and meta-analysis, the mortality was 0.96 (95% CI [0.67-1.4]) per 100 person-years after embolization for all S–M grades of AVM. Permanent neurological deficits or death occurred in a median 6.6% (range, 0–28%) of patients after embolization. Moreover, obliteration was achieved in only a median of 13% (range, 0–94%) after embolization was used as a single modality.<sup>17)</sup> Potts et al.<sup>18)</sup> conducted a literature review on the use of embolization to cure AVMs, and the mortality and significant morbidity rates (permanent neurological deficits or clinically confirmed hemorrhages) were 0–4.3% and 0–22%, respectively, for all AVMs. In their review, an association between low S–M grades and complete embolization was suggested.<sup>18-21)</sup>

Although there are not many reports of curing S–M Grade III AVMs using endovascular treatment as a single modality, Dumont et al.<sup>22)</sup> reported the results of endovascular treatments (including Onyx) used with the goal of AVM obliteration. The complication and mortality rates for S–M Grade III AVMs were 23% and 0%, respectively. However, embolization used alone did not achieve complete obliteration in S–M Grade III AVMs in their series.

Pandey et al.<sup>9)</sup> reported the outcomes of embolization in their multimodal treatment series. The incidence of neurological complications after embolization was 2.3% per procedure and 5.2% per patient, whereas the incidence of major complications was 0.6% per procedure and 1.3% per patient.

Crowley et al.<sup>23)</sup> also reported 327 patients treated using embolization as a part of a multimodal treatment strategy, but the S–M grade was not associated with any differences in outcome. Their series included the embolization materials, Onyx and *N*-butyl cyanoacrylate (NBCA). Permanent neurological deficits were observed in 13% of S–M Grade III AVMs. Furthermore, there were no statistically significant differences between Onyx and NBCA with regard to any of the outcome variables.

The endovascular techniques employed will be quite different if the treatment goal is cure rather than palliative or targeted embolization. However, at the moment, the rate of complete obliteration by embolization alone is insufficient, and curative embolization has played a very minor role in treatments. We have to consider the risk of incomplete efficacy and post treatment hemorrhage and recanalization for S–M Grade III AVMs.<sup>17,18)</sup>

### Radiosurgery for S–M Grade III AVMs

The mortality reported in a systematic review and meta-analysis of AVMs from all S–M grades was 0.50 (95% CI [0.43–0.58]) per 100 person-years after stereotactic radiosurgery (SRS). Permanent neurological deficits or death occurred in a median 5.1% (range, 0–21%) of patients after SRS.<sup>17)</sup>

Yamamoto et al.<sup>24)</sup> reported a gamma knife radiosurgery series in which the overall rate for complete obliteration was 65%, while the complete obliteration rate for S–M Grade III AVMs alone was 74% and was not greatly different. Conversely, Friedman et al.<sup>25)</sup> reported a poor obliteration rate for S–M Grade III AVMs (35.7%) following radiosurgery. However, care must be taken in evaluating the obliteration rate in a radiosurgical management series. The definitions of obliteration and morbidity, and the follow-up periods were different in each study.

Andrade-Souza et al.<sup>14)</sup> modified S–M Grade III to Grade IIIA (>3 cm) and IIIB (<3 cm). The obliteration rate for Grade IIIB was 67.3% and for Grade IIIA was 53.3%. Radiation-induced complications occurred in 25% of patients with Grade IIIB, and 26.7% with Grade IIIA. These researchers concluded that the RBAS can reliably be used to predict the results following a single radiosurgical treatment, and the modified S–M grade can also predict the radiosurgical results.

The use of radiosurgery for S–M Grade III AVMs may be less effective compared with lower grade AVMs. Thus, the rate of complete obliteration using radiosurgery for S–M Grade III AVMs is not adequate compared with surgical results. Moreover, it has been found that a certain hemorrhage risk occurs during latency periods and the adverse radiation effects remain, although the risk of hemorrhage during the latency period is not higher than that for the natural history.<sup>26,27)</sup> Therefore, a radiosurgical multimodal strategy with embolization or surgery has been considered a reliable treatment to improve the outcome.

### Multimodality Treatment Strategy for S–M Grade III AVMs

Multimodal treatment includes 1) microsurgery with or without embolization, 2) radiosurgery with or without embolization, and 3) a combination of these techniques. Although it is difficult to generalize information on multimodal treatments, it is expected to play a helpful role in treating S–M Grade III AVMs.<sup>5)</sup>

#### Surgical series with or without embolization

Although S–M Grade III AVMs are sometimes treated by surgical resection as a single modality, many cases are treated by surgical resection following preoperative embolization. In a surgical series with or without embolization, the rate of total obliteration was reported as 88–100%. The total morbidity rates and the permanent morbidity rates were 13–56% and 4–17%, and the mortality rate was 0–4%.<sup>10–13,28–35)</sup>

De Oliveira et al.<sup>12)</sup> first classified Grade III to Grade IIIA (large size) and IIIB (small size in eloquent areas). In their series, the total resection rate was 97–100% in S–M Grade III AVMs. The morbidity rate was 21.9%, and the morbidity was significantly higher in Grade IIIB than Grade IIIA.

Schaller et al.<sup>30)</sup> reported the results of microsurgical resection that included preoperative embolization. The overall surgical morbidity was 15.3% for all AVMs. For Grade III AVMs, the surgical morbidity was 25.0% and the outcomes were less favorable. From their results, a significant correlation was suggested between the eloquence of the AVM localization and the surgical morbidity. They also proposed that the eloquence of the S–M grading scale should be divided into “highly eloquent” (brainstem, basal ganglia, or precentral cortex) and “less eloquent” (for example, the visual cortex), which is important for risk analysis.

Surgical results including preoperative embolization for S–M Grade III AVMs have also been reported by

Hartmann et al.<sup>31)</sup> At long-term follow-up, surgery-related neurological deficits were found in 32% of patients (4% disabling, 28% non-disabling). The mortality rate was 0%. In the series of Lawton,<sup>11)</sup> the rate of complete surgical obliteration with preoperative embolization was 97.4%. The permanent, treatment-associated neurological morbidity was 3.9% and the surgical mortality was 3.9%.

Preoperative embolization with Onyx has been increasingly practiced for AVM resection. A decrease in complications and improvement in outcomes can be expected by eliminating difficult surgical areas and reducing the intraoperative bleeding and operation times.<sup>36)</sup> This makes it possible to resect the nidus more closely. On the other hand, Morgan et al.<sup>37)</sup> reported that the outcomes of AVM surgery were not improved by preoperative Onyx embolization. With respect to preoperative embolization for S–M Grade III AVMs, adverse outcomes were reported in 5.23% (95% CI [2.64–9.78]) of S–M Grade III AVMs in their series. The adverse outcomes for S–M Grades I and II AVMs were lower, at 0.34% in their series. In the period after the introduction of Onyx, the rate of adverse outcomes for Grade III AVMs was unchanged at 5.4%. Although the usefulness of Onyx has also been reported, no clear-cut benefit has yet been demonstrated.<sup>37)</sup>

Jeon et al.<sup>10)</sup> reported that the rate of surgical obliteration was 89.1%. In their series, preoperative embolization with NBCA and Onyx was included as adjunctive therapy. The immediate procedure-induced morbidity rate was 12.7% and the permanent deficit rate was 5.5%. The mortality rate was 0%. The size of the AVM and a non-hemorrhagic type were associated with procedural risk.

Because of preoperative embolization with recent technological advances, the surgical results for S–M Grade III AVMs have shown an improving trend. However, the results were not significant.<sup>3,10,11,16)</sup> The evidence is also not sufficient to verify which embolic material is more effective for preoperative embolization: Onyx or NBCA.

For unruptured S–M Grade III AVMs, there are a few reports on multimodal treatment results. Bervini et al.<sup>32)</sup> reported a more multimodal strategy for the surgical treatment of unruptured S–M Grade III AVMs compared with the ARUBA study. They used the classification system of Spetzler–Ponce, Class B. Fourteen percent developed a new, permanent neurological deficit with a modified Rankin scale (mRS) score of >1, and 2.8% experienced new, permanent neurological deficits with mRS >2 at the last follow-up. They concluded that surgical treatment produced a better outcome than conservative management of patients with unruptured Grade III

AVMs where the outcome is considered to be mRS >2. Following that, they concluded that most of the ruptured and unruptured Spetzler–Ponce Class A and B AVMs can be treated surgically with a low risk of permanent morbidity and a high likelihood of preventing future hemorrhage.<sup>38)</sup>

Morgan et al.<sup>34)</sup> also reported surgical results for unruptured S–M Grade III AVMs, and the complete obliteration rate was 96%. Adverse outcomes or near misses (irrespective of the outcome mRS) occurred in 32% of patients. New permanent neurological deficits leading to a mRS of >1 occurred in 21% of patients. Major morbidity leading to a mRS of >2 (including mortality) occurred at a rate of 3.6%. The AVM size, deep venous drainage, and an eloquent location produced no significant difference in the risk for either an adverse outcome or a near miss, or an adverse outcome with a new, permanent neurological deficit and a mRS of >1.

### I. Radiosurgical series with or without embolization

In several radiosurgical series with or without embolization, total obliteration was reported in 36–86% of S–M Grade III AVMs, although the follow-up periods were different in each report. The rates for total morbidity and permanent morbidity were 6–23% and 3–7%, respectively. The mortality rates were 0.5–4.2%.<sup>25-27,39-41)</sup>

Gobin et al.<sup>39)</sup> reported the combined use of embolization (NBCA and cyanoacrylate) and radiosurgery for S–M Grade III AVMs. The cure rate was 71%. The morbidity (permanent neurological deficit) and the mortality were 5% and 2.5%, respectively. There were no complications associated with radiosurgery. Meder et al.<sup>40)</sup> reported the response to radiosurgery according to the S–M grading scale. Although subtotal resection, embolization, resection and embolization, and radiosurgery were included as prior treatments, the obliteration rate for S–M Grade III AVMs was 68.4%.

Radiosurgical series reported by Ding et al. resulted in total obliteration rates for S–M Grade III AVMs of 69% a median 46 months after radiosurgery.<sup>26)</sup> Two patients (0.5%) died of hemorrhage during the radiosurgical latency period. The rates of symptomatic and permanent radiation-induced changes (RIC) after radiosurgery were 12% and 4%, respectively. They also reported radiosurgical results for low-grade AVMs, and the rates of symptomatic and permanent post-radiosurgical RIC were 8.2% and 1.4%, respectively. The S–M Grade III outcomes were unfavorable compared with those of low-grade AVMs.<sup>26,42)</sup>

Kano et al.<sup>27)</sup> reported total obliteration rates of 48% at 3 years, 69% at 4 years, 72% at 5 years, and 77%

at 10 years (a mean follow-up period of 89 months). Symptomatic adverse radiation effects (AREs) were detected in 6% of patients and permanent symptomatic AREs were detected in 2.7% (at a median of 13 months). The morbidity rate was 4.2%. The annual hemorrhage rate was 2.7% after SRS and the mortality rate due to AVM hemorrhage after SRS was 4.2%. The annual hemorrhage rates without obliteration were 2.6% in the first year, 1.9% at 1–2 years, 1.1% at 2–3 years, 0.9% at 3–5 years, and 0.6% at 5–10 years.

Koltz et al. reported the long-term outcome of radiosurgery for S–M Grade III AVMs with more than 5 years of follow-up.<sup>41)</sup> Their series included staged SRS and embolization with NBCA or Onyx. The obliteration rate was 86% and this outcome was better than any previously reported series. The combination of embolization and staged SRS might produce good results. The morbidity rate was 23% (minor 16%, major 7%), which was not higher than their results for low-grade AVMs (morbidity rate: 20% for S–M Grade I, 29% for S–M Grade II). Radiosurgery combined with embolization may offer favorable outcomes with relatively low morbidity for S–M Grade III AVMs.

Conversely, some reports have indicated that SRT with embolization is less effective than radiosurgery alone. Some authors have reported that embolization prior to radiosurgery may reduce the obliteration rate.<sup>43)</sup> The risk-to-benefit of embolization combined with radiosurgery remains controversial and the optimal timing of obliteration with respect to radiosurgery also remains an unresolved issue.<sup>44–46)</sup>

## II. Combination of microsurgery, embolization, and radiosurgery

As a multimodal treatment for S–M Grade III AVMs, combination strategies have also been reported. Complete obliteration was reported in 65–96% of cases. The rates for total morbidity and permanent morbidity were 8–30% and 5–20%, respectively. The mortality rate was 0–4.7%.<sup>9,29,35,47,48)</sup>

Deruty et al.<sup>29)</sup> reported that complete obliteration was achieved in 88% of patients. The morbidity rate was 35% (transient neurological deficits in 29%, permanent neurological deficits in 6%), and the mortality rate was 0%.

The use of a multimodal treatment strategy for 100 patients with S–M Grade III AVMs was reported by Pandey et al.<sup>9)</sup> The total obliteration rate was 87.6%, the morbidity rate (new neurological deficits) was 14% (5% disabling, 9% non-disabling), and the mortality rate was 1%. From their results, older age (>40 years), an AVM size of >3 cm, and a non-hemorrhagic presentation were reported as a predictors of new deficits. A location in eloquent

cortex and the presence of venous drainage did not confer any benefits.

Nerva et al.<sup>48)</sup> reported ARUBA-eligible unruptured S–M Grade III AVMs treated using a multimodal strategy. There was no mortality and the rate for major complications was 30%. Persistent neurological deficits and transient deficits after treatment were found in 20% and 10% of patients, respectively. From their surgical results with or without embolization, major complications were observed in 56% (persistent neurological deficits in 33% and transient deficits in 22%) despite achieving a high rate of obliteration. From their radiosurgical results with or without embolization, major complications occurred in 9% of patients (all with persistent neurological deficits, and none with transient deficits). These rates were an improvement on the surgical results; however, the cure rate was 67% with follow-up for more than 2 years.

## Subtypes of S–M Grade III AVMs

The S–M Grading scale is composed of three elements: size (S), location in eloquent cortex (E), and the presence of deep venous drainage (V). S–M Grade III AVMs in particular are known as a heterogeneous group consisting of four subtypes: S1E1V1, S2E0V1, S2E1V0, and S3E0V0. The treatment results and outcomes for each subtype of S–M Grade III AVMs have been investigated to evaluate the risk associated with each subtype (Table 1).

Lawton<sup>11)</sup> reported that the surgical risk differs greatly for S1E1V1 (2.9%), S2E0V1 (7.1%), and S2E1V0 (14.8%), but the risk for S3E0V0 was unknown. They suggested that S1E1V1 and S2E0V1 could be treated safely using microsurgery, and S1E1V1 AVMs have a similar surgical risk compared with low-grade AVMs. Furthermore, the S2E1V0 subtype required more conservative management and surgical therapeutic indications must be considered carefully for S–M Grade III AVMs.

Moreover, Jeon et al.<sup>10)</sup> also reported the surgical outcomes of S–M Grade III AVMs according to the modified grading system of Lawton.<sup>11)</sup> Their overall immediate procedure-induced morbidity after microsurgery was 12.7%, and the permanent deficit was 5.5% with no mortality. However, the morbidity differed for each subtype. Immediate deficits were observed in 0% of patients with S1E1V1, 12.5% with S2E0V1, 25.0% with S2E1V0, and 0.0% with S3E0V0. All patients with mild deficits recovered after 6 months, but permanent procedure-induced disability was remained in only S2E1V0. The S2E0V1 and S2E1V0 subtypes are associated with relatively unfavorable tendencies. These results support the

**Table 1 Overview of published series. The treatment results for subtypes of Spetzler–Martin Grade III AVMs**

Authors year	Lawton et al.* 2003	Davidson et al.† 2010	Pandey et al.* 2012	Kano et al.§ 2014	Ding et al.¶ 2014	Jeon et al.** 2014
	Surgical series	Surgical series	Multimodal strategy	Radiosurgical series	Radiosurgical series	Surgical series
Total (n)	76	169	100	474	398	55
Morbidity (%)	3.9	9	14	6.3/2.7	12/4	12.7/5.5
Mortality (%)	3.9	6.5	1	0.2	0.5	0
S1E1V1 (n)	35	32	28	282	302	18
Obliteration (%)	100	NR	NR	74	69	94.4
Morbidity (%)	2.8	9.3	3.6	6.7/3.5	NR	0/0
Mortality (%)	2.8	NR	0	NR	NR	0
S2E0V1 (n)	14	52	11	44	35	16
Obliteration (%)	92.8	NR	NR	72	27	87.5
Morbidity (%)	7.1	15.3	9.1	6.8/0	NR	12.5/0
Mortality (%)	0	NR	NR	NR	NR	0
S2E1V0 (n)	27	79	60	148	61	20
Obliteration (%)	96.2	NR	NR	69	35	85
Morbidity (%)	14.8	15.1	18.3	5.4/2	NR	25/15
Mortality (%)	7.4	NR	NR	NR	NR	0
S3E0V0 (n)	0	6	1	0	0	1
Obliteration (%)	NA	NR	NR	NA	NA	100
Morbidity (%)	NA	16.6	100	NA	NA	0/0
Mortality (%)	NA	NR	0	NA	NA	0

NR: not reported, NA: not applicable, \*Morbidity: permanent new deficit or death, †Morbidity: risk of adverse outcome due to surgery, ‡Morbidity: new neurological deficits, Mortality after multimodality management was 1% (one patient), but subtype could not be identified, §Morbidity: adverse radiation effects (symptomatic/permanent). Obliteration rate represents 5-year total obliteration, ¶Morbidity: radiation-induced changes (symptomatic/permanent), Mortality: two patients died of postradiosurgery hemorrhage, Obliteration rate represents 5-year total obliteration, \*\*Morbidity: newly developed neurological deficits (immediate/permanent).

usefulness of Lawton's modified grading system to predict the surgical morbidity and the clinical outcome of S–M Grade III AVMs.

The microsurgical risk of adverse events associated with the subtypes of S–M Grade III AVMs were reported by Davidson and Morgan<sup>13)</sup> as follows: 9.3% for S1E1V1, 15.3% for S2E1V0, 15.1% for S2E0V1, and 16.6% for S3E0V0. Their treatment included preoperative embolization, and the S1E1V1 subtype had lower surgical morbidity, as indicated by other authors.

Pandey et al.<sup>9)</sup> reported an overall obliteration rate of 87.6% using multimodal management, and the overall morbidity rate (for new neurological deficits) was 14% for all S–M Grade III AVMs.

The complication rates for the four subtypes were as follows: 3.6% for S1E1V1, 9.1% for S2E0V1, 18.3% for S2E1V0, and 100% for S3E0V0. The mortality rate was 1%. In their series, younger age (<40 years), smaller size (<3 cm), S1E1V1 subtype, and hemorrhagic presentation were associated with significantly lower rates of new neurological deficits with treatment. In their study, the size of the AVM was associated with neurological complications, but an eloquent location and venous drainage were not.

Kano et al.<sup>27)</sup> reported the radiosurgical results for each subtype. They reported an overall morbidity rate of 5.5% and a mortality rate of 4.2%. Although 6.3% of patients developed symptomatic AREs, there was no association between subtypes and AREs. AREs

leading to permanent neurological deficits occurred in 3.5% of patients with S1E1V1, 0% with S2E0V1, and 2% with S2E1V0. S3E0V0 was not included in the study. Moreover, the 5-year total obliteration rates after SRS were 74% for S1E1V1, 72% for S2E0V1, and 69% for S2E1V0. Twelve percent of patients underwent additional SRS. Notably, they reported cumulative 5-year hemorrhage rates of 4.9% for S1E1V1, 14.9% for S2E0V1, and 7.6% for S2E1V0. The cumulative rate of hemorrhage was significantly higher in S2E0V1.

Ding et al.<sup>26)</sup> also reported radiosurgical results for S–M Grade III AVMs subtypes. The rate for symptomatic RIC was 12% and permanent RIC was 4.0%. Although the presence of a single draining vein was significantly associated with RIC, the subtype was not. Conversely, a lower S–M Grade III subtype was significantly associated with AVM obliteration following radiosurgery. Moreover, the actual obliteration rates were significantly higher for S1E1V1. They concluded that small S–M Grade III AVMs located in eloquent cortex with deep venous drainage are good treatment targets for radiosurgery. In their study, the annual hemorrhage rate for Grade III AVMs after radiosurgery was 1.7%, and it did not exceed the hemorrhage rate for natural history.<sup>12,49)</sup>

## Discussion

Although multimodal treatment of S–M Grade III AVMs is recommended, the clinical risks and clinical outcomes were different for each subtype. Moreover, the outcomes and risks were also different for each treatment modality.<sup>9,11,26,27)</sup> We should be aware of the treatment risk for each subtype and select the safest modality. As well as the S–M grading system, other grading systems may also be useful, such as the Buffalo score<sup>22)</sup> to evaluate the embolization risk, the AVM embolization prognostic score developed by Starke et al.,<sup>50)</sup> and the Flickenger–Pollock RBAS<sup>15)</sup> to predict the obliteration of AVMs. Moreover, use of these scoring systems may improve the multimodal treatment effect.

S–M Grade III AVMs have to be evaluated based on the individual AVM grading components and the clinical symptoms. Lawton et al.<sup>51)</sup> reported that the resection of S–M Grade III AVMs using a multimodal treatment strategy confers a 30% risk of neurological deterioration. They proposed a modification of the AVM grading system in the form of a supplementary grading scale based on patient age, hemorrhagic presentation, and AVM diffuseness, to predict neurological outcomes after surgery. By adding the previous S–M grading score and this supplementary grading score into a combined grading

scale, the score ranges from 1 to 10. With this scale, the grading can be classified more finely. The supplementary grading scale may influence surgical decisions for patients with AVM at the borderline between high and low risk.<sup>51)</sup>

According to previous reports, S1E1V1 might indicate a therapeutic group that is associated with lower morbidity and greater efficacy in both surgical and radiosurgical series. Furthermore, S1E1V1 has a similar surgical risk compared with low-grade AVMs, and is a good indication that surgery will achieve high levels of obliteration.<sup>9–11,13,26,27)</sup> Moreover, Kano et al. and Ding et al. concluded that the S1E1V1 subtype was more likely to be obliterated by radiosurgery.<sup>26,27)</sup> Thus, the S1E1V1 subtype might represent a good therapeutic group for radiosurgery.

Although the risk of hemorrhage remains during the latency period, a radiosurgical treatment strategy might be preferable to surgical treatment for the S2E1V0 subtype because of the high rate of surgical morbidity, despite the high curability.<sup>10,11,26,27)</sup>

The S2E0V1 subtype may still be an intermediate surgical treatment group. However, the cumulative hemorrhage rate after radiosurgery was reportedly higher for the S2E0V1 subtype than for other subtypes.<sup>27)</sup> Thus, a surgical treatment strategy might be more suitable. For the S3E0V0 subtype, sufficient treatment results have not yet been reported, and it is difficult to evaluate the treatment outcome. Since a hemorrhagic presentation has been reported as a predictor of lower morbidity with treatment,<sup>9)</sup> hemorrhagic presentation may increase the possibility of high surgical risk subtypes being treated safely. At the moment, the number of reported outcomes from the use of embolization as a single modality for S–M Grade III AVMs is extremely small. Thus, a further report would be useful.

The sub-classification of S–M Grade III AVMs is useful for selecting the appropriate treatment modality, and adopting a multimodal treatment strategy must have a true potential that is yet to be fully realized. The results of treatments for S–M Grade III AVMs have not yet been reported thoroughly enough to satisfy the establishment of criteria, despite recent technological advances in surgery. Further reports limited to a specific subtype would be expected. The S–M Grade III AVMs still present a therapeutic challenge, even with multimodal treatments.

## Conflicts of Interest Disclosure

The authors have no disclosures to report.

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