Article published online: 2024-12-11

An Algorithm for the Multimodality Treatment of Cerebral Arteriovenous Malformations

Um algoritmo para o tratamento multimodal de Malformações Arteriovenosas Cerebrais

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Arq Bras Neurocir 2024;43(4):e286–e295.

Abstract

Introduction: The algorithm of multimodal treatment (MMT) of arteriovenous malformations (AVMs) combined with intent-to-cure and presurgery embolization benefits was developed. **The aim** was to analyze the effectiveness of the MMT compared with unimodal intent-to-cure embolization in patient groups matched concerning clinical and angiographic characteristics.

Methods: A prospective cohort study of MMT effectiveness and safety was performed. To estimate differences in the total occlusion rate and complication rate of MMT compared to unimodal embolization, a 1:1 matched patient group was identified from the Russian Endovascular Neuro Society (RENS) AVM registry using the propensity score matching (EMB group). The treatment outcomes were assessed by the rate of achieving 100% AVM obliteration on follow-up angiography, morbidity, mortality, and the perioperative complication rate.

Results: Complete AVM occlusion was achieved in 93.7% of patients in the MMT group vs 76.2% of patients in the EMB group ($p < 0.001$). A favorable clinical outcome ($mRS = 0–1$ at the end of follow-up) was observed in significantly more patients in the MMT group compared with the EMB group (88.9% vs 71.4%, $p = 0.024$). In the MMT group, the rates of intraoperative and postoperative ischemic complications were comparable to those in the EMB group, and there was a significantly lower rate of postoperative hemorrhagic complications (6.3% vs 20.6%, $p = 0.035$).

Conclusions: Embolization as the main curative technique of the multimodal algorithm timely followed by microsurgery and radiosurgery ensures the highest clinical

Keywords
► malformation

received
November 7, 2023
accepted
October 18, 2024

DOI https://doi.org/10.1055/s-0044-1795069.
ISSN 0103-5355.

and angiographic efficacy of treatment and reduces the rate of disabling postoperative complications.

Resumo

Introdução: O algoritmo de tratamento multimodal (MMT) de malformações arteriovenosas (MAVs) combinado com os benefícios da embolização com intenção de cura e pré-cirurgia foi desenvolvido. O objetivo era analisar a eficácia da MMT em comparação com a embolização com intenção de cura unimodal em grupos de pacientes pareados em relação às características clínicas e angiográficas.
Métodos: Um estudo de coorte prospectivo da eficácia e segurança da MMT foi realizado. Para estimar as diferenças na taxa total de oclusão e na taxa de complicação da MMT em comparação com a embolização unimodal, um grupo de pacientes pareado 1:1 foi identificado no registro de MAV da Russian Endovascular Neuro Society (RENS) usando a correspondência de pontuação de propensão (grupo EMB). Os resultados do tratamento foram avaliados pela taxa de obtenção de 100% de obliteração da MAV na angiografia de acompanhamento, morbidade, mortalidade e taxa de complicação perioperatória.
Resultados: A oclusão completa da MAV foi alcançada em 93,7% dos pacientes no grupo MMT vs 76,2% dos pacientes no grupo EMB ($p < 0,001$). Um resultado clínico favorável (mRS = 0–1 no final do acompanhamento) foi observado em significativamente mais pacientes no grupo MMT em comparação com o grupo EMB (88,9% vs 71,4%, $p = 0,024$). No grupo MMT, as taxas de complicações isquêmicas intraoperatórias e pós-operatórias foram comparáveis às do grupo EMB, e houve uma taxa significativamente menor de complicações hemorrágicas pós-operatórias (6,3% vs 20,6%, $p = 0,035$).
Conclusões: A embolização como a principal técnica curativa do algoritmo multimodal seguida oportunamente por microcirurgia e radiocirurgia garante a mais alta eficácia clínica e angiográfica do tratamento e reduz a taxa de complicações pós-operatórias incapacitantes.

Palavras-chave
► malformação

Introduction

Arteriovenous malformations (AVMs) of the brain are complex lesions characterized by a tortuous vascular bundle located between one or more feeding arteries and one or more draining veins.[1] The incidence rate of newly diagnosed AVMs ranges from 1[2] to 1.34 (3) per 100,000 population per year, of which about half are malformations with hemorrhagic presentation.[3,4] Only a small number of intact AVMs result in neurological deficits; however, after rupture, neurological deficits of varying severity are present in 30–50% of cases,[5] which necessitates timely diagnosis and treatment of AVMs to reduce the risk of disability. Despite the rapid development of endovascular techniques, which improves the clinical and angiographic outcomes of treatment each year, there are still some disputes about their applicability for certain groups of patients[6] and about correct combinations of modalities to achieve the maximum efficacy and safety of surgical treatment.[7–10]

The first and most important problem is the management of patients with unruptured AVMs. Surgical treatment is considered conditionally mandatory for patients with ruptured AVMs[11] due to a significantly increased risk of rerupture and mortality.[12] However, the management of unruptured AVMs (especially asymptomatic) is still contradictory.[13,14] This is largely related to the inability to assess real risks of a natural course of the disease because a high number of patients are unaware of their AVMs (in this group, both silent AVMs and, on the contrary, the most severe AVMs in which the first rupture leads to immediate death) and because disparate groups are often compared. In this case, most neurosurgical centers are required to offer treatment to AVM patients, which consistently updates statistics on the treatment of different AVMs.

The second important problem is the choice of optimal surgical management. Currently, there are three surgical options: microsurgery, endovascular embolization, and radiosurgery.[1] Each of them has its own advantages and disadvantages, so their combinations, i.e. multimodal treatment,[15] are usually used, depending on characteristics of the patient and AVM. However, there are different approaches to multimodal treatment, which vary depending on the surgeon's preferences, current clinical guidelines, and protocols.[16,17] The question of how to combine them correctly and, most importantly at the moment, how embolization should be optimally used remains unresolved.[18] In this regard, there are two extreme opinions: consider embolization primarily as an adjuvant option to reduce the AVM size and facilitate subsequent microsurgery or radiosurgery[19,20] or consider it as a stand-alone and main option with intent to cure and to embolize up to the maximum occlusion.[12,19,21] At the start of the AVM registry of the Russian Endovascular Neuro Society (RENS), the second option was initially adopted. The 6-year experience in treating more than 500 AVMs, a gradual modification of the surgical approach, and increasing competence in radiosurgery and microsurgery have prompted us to conclude that embolization should be considered as the main curative modality combined with microsurgery or radiosurgery to improve safety and long-term clinical outcomes, which provides a third option for its use, rarely considered in the literature. Based on this option, we developed and implemented an algorithm for multimodal management of AVM patients, which accounts for the main advantages and limitations of each of the modalities. The aim of this study was to analyze the efficiency of the implemented algorithm for multimodal treatment of cerebral AVMs compared with that of the monomodal intent to cure use of embolization in groups of patients comparable in clinical and anatomical characteristics of AVMs, who were selected using the propensity score matching (PSM) method.

Methods

Study Design and Patient Selection

We performed a prospective cohort study of multimodal treatment with a comparison group selected from the RENS AVM registry. The study included 562 patients with intracranial AVMs who received endovascular treatment at the Centre for Angioneurology and Neurosurgery of the Meshalkin National Medical Research Center in the period between 2009 and 2019 and at the Federal Center of Brain Research and Neurotechnologies of the FMBA in the period between 2021 and 2022. Starting in 2011, multimodal treatment of AVM patients, with continuous efficiency evaluation, was introduced. All patients who agreed to participate in the study were included in the multimodal treatment group (MMT group, n = 75).

The criteria for inclusion in the MMT group were as follows:

- age below 75 years;
- technical feasibility of endovascular treatment;
- impossibility of complete one-stage AVM embolization;
- signed informed consent to participate in the study.

The exclusion criteria were:

- history of AVM rupture within the last 30 days;
- clinical and neurological instability of the patient within 24 hours before surgery;
- indications for palliative treatment (subtentorial AVM, Spetzler–Martin grade 5 AVM);
- severe comorbidity.

The comparison group (endovascular embolization (EMB) alone) was selected from 220 patients who underwent endovascular embolization alone, completed treatment, and followed up for at least 6 months with control angiography. After excluding patients with 100% occlusion after the first stage of embolization as not comparable with patients of the MMT group, 127 patients of the embolization group were allocated to the comparison group and included in the analysis. To eliminate differences between the groups and potential bias in the selection of patients, comparable groups were selected using the PSM method. The final groups included 63 patients each (►**Table 1**).

Principles of Endovascular Embolization

Based on our previous studies of hemodynamic models of AVM embolization and clinical experience, we set up the following embolization principles which have been adhered to regardless of whether the patient belongs to the MMT or embolization group:

- AVM closure is performed using intranidal embolization and is not limited to the closure of feeding arteries;
- Use of a catheter with a distal detachable tip;
- Treatment begins with elimination of a fistula component;
- Along with fistula components, AVM compartments with intranidal aneurysms, as potential sources of hemorrhagic complications, are first eliminated;
- Tendency for radicality without increasing the risk of complications;
- Multistage embolization with no more than 60% occlusion in one stage is preferable to decrease the risk of sudden changes in AVM hemodynamics;
- Feeding arteries should be closed starting from large to small vessels.

Treatment Protocol and Ethics

For patients included in the MMT group, the individual treatment approach was defined based on monitoring the patient's condition after each of the surgical stages with additional, if necessary, radiosurgery or microsurgery after one or more stages of embolization. Embolization included 1 to 11 stages to comply with the identified principles of curative embolization while minimizing the risk of procedures. The study was conducted according to good clinical practice, which ensures that the design, implementation, and communication of data are reliable, that patient's rights are protected, and that the integrity of subjects is maintained by the confidentiality of their data. The study was approved by the Local Ethics Committee of the Meshalkin National Medical Research Center (number of protocols 15, September 3, 2009). All patients provided written informed consent by the Declaration of Helsinki, which included their consent for using their data in analyses and for it to be presented.

Data Collection

At enrollment, information on disease history, characteristics, and severity was collected for each patient. Data about the disease onset, clinical course, and complete preoperative neurological status were considered. Preoperative non-

Table 1 Comparative characteristics of patients with multimodal treatment and embolization before and after selection of comparable groups using the PSM method

Parameter	Before PSM			After PSM		
	EMB (n = 127)	MMT (n = 75)	P value	EMB (n = 63)	MMT (n = 63)	P value
Gender: female, n [%]	62 [48.82%]	41 [54.67%]	0.511	34 [53.97%]	32 [50.79%]	0.858
Age of onset, Me (IQR)	28 (21 : 40)	27 (17 : 42)	0.668	28 (20.5 : 42)	25 (16 : 40)	0.393
Age at treatment, Me (IQR)	35 (24.5 : 45.5)	36 (24 : 47.5)	0.996	35 (25 : 47)	32 (22 : 45)	0.481
Disease duration, Me (IQR)	1 (0 : 5.5)	2 (0.5 : 6)	0.214	1 (0 : 6.5)	2 (1 : 5.5)	0.294
Primary symptom, n [%] Asymptomatic Headache Neurological deficit Seizure Intracranial hemorrhage	 4 [6.35%] 11 [17.46%] 2 [3.17%] 22 [34.92%] 24 [38.1%]	 3 [4.76%] 6 [9.52%] 1 [1.59%] 23 [36.51%] 30 [47.62%]	0.624	 11 [8.66%] 20 [15.75%] 6 [4.72%] 43 [33.86%] 47 [37.01%]	 5 [6.67%] 9 [12%] 1 [1.33%] 24 [32%] 36 [48%]	0.495
mRS score, n [%] 0 1 2 3 4 5	 106 [83.46%] 15 [11.81%] 3 [2.36%] 3 [2.36%] 0 [0%] 0 [0%]	 59 [78.67%] 9 [12%] 3 [4%] 1 [1.33%] 2 [2.67%] 1 [1.33%]	0.317	 49 [77.78%] 11 [17.46%] 1 [1.59%] 2 [3.17%] 0 [0%] 0 [0%]	 50 [79.37%] 7 [11.11%] 3 [4.76%] 1 [1.59%] 1 [1.59%] 1 [1.59%]	0.516
Spetzler–Martin grade, n [%] I II III IV	 5 [3.94%] 39 [30.71%] 62 [48.82%] 21 [16.54%]	 5 [6.67%] 20 [26.67%] 35 [46.67%] 15 [20%]	0.72	 3 [4.76%] 18 [28.57%] 29 [46.03%] 13 [20.63%]	 2 [3.17%] 18 [28.57%] 30 [47.62%] 13 [20.63%]	0.975
Localization: involvement of two or more brain areas, n [%]	25 [19.69%]	18 [24%]	0.585	17 [26.98%]	16 [25.4%]	>0.999
Localization: eloquent brain area, n [%]	22 [57.89%]	13 [61.9%]	0.981	12 [54.55%]	11 [64.71%]	0.755
Cysts associated with AVM, n [%]	25 [19.69%]	20 [26.67%]	0.328	12 [19.05%]	18 [28.57%]	0.296
Presence of a fistula component, n [%]	50 [39.37%]	25 [33.33%]	0.479	22 [34.92%]	20 [31.75%]	0.85
Aneurysms associated with AVM, n [%]	35 [55.6%]	14 [22.2%]	**0.002**	17 [26.98%]	14 [22.22%]	0.679
Transient afferents, n [%]	30 [26.79%]	36 [50.7%]	**0.002**	18 [30.51%]	28 [47.46%]	0.089
Caliber of AVM vessels, n [%] Small Mixed Medium Large	 13 [14.94%] 32 [36.78%] 6 [6.9%] 36 [41.38%]	 20 [33.9%] 15 [25.42%] 6 [10.17%] 18 [30.51%]	**0.035**	 11 [22.92%] 17 [35.42%] 6 [12.5%] 14 [29.17%]	 11 [23.4%] 14 [29.79%] 5 [10.64%] 17 [36.17%]	0.882
Venous drainage, n [%] Superficial Mixed Deep	 75 [59.06%] 19 [14.96%] 33 [25.98%]	43 [57.33%]	0.078	 32 [42.67%] 15 [20%] 28 [37.33%]	 26 [41.27%] 11 [17.46%] 26 [41.27%]	0.135
Maximum AVM size, cm, Me (IQR)	36 (29 : 44)	35 (28 : 45)	0.581	35.5 (30 : 43.5)	35 (29 : 46)	0.895

invasive neuroimaging (CT, MRI) was used to assess the AVM size and localization, eloquence of the brain area, and Spetzler–Martin grade.[22] If there were signs of previous hemorrhage (posthemorrhagic cysts, hemosiderin deposits), the type of disease course was assessed as hemorrhagic. Preoperative panangiography was performed, which involved selective angiography of both carotid territories (internal carotid arteries (ICAs) and external carotid arteries (ECAs) separately) and the vertebrobasilar territory (both vertebral arteries). Angiography data were used to evaluate malformation vascular territories, the number, type (terminal, transient), and diameter of feeding arteries, the presence of flow-related or unrelated aneurysms, their type, location, number, and size, the presence of a fistula component, the caliber of AVM nidus vessels, the number of veins, the type (deep, superficial) of venous drainage, and the presence of varices.

Endpoint Definition

The primary endpoint of the study was 100% AVM obliteration on follow-up angiography scans after the last surgical stage.

The secondary endpoints of the study were:

- 90% or more (subtotal) malformation occlusion according to follow-up angiography;
- neurological outcomes in patients: the number of patients with different dynamics of neurological deficit (achievement or maintenance of the mRS; an increase in the mRS by 1 or more points; achievement of the mRS = 2 or more; an increase in the mRS by 2 or more points);
- development of complications associated with AVM surgery during postoperative hospital stay: the total number of complications (any technical complication) and the number of complications leading to deterioration in the patient's condition (a persistent decrease in the mRS by at least 1 point, which was not compensated until discharge from the hospital);
- mortality in the early postoperative period.

Statistical Analysis

The STATISTICA 7.0 software (StatSoft, USA) and RStudio software version 1.0.136 (Free Software Foundation, Inc., USA) with R packages version 3.3.1 (R Foundation for Statistical Computing, Austria) were used for analyses.

Descriptive statistics were shown as absolute frequencies or medians with interquartile range. The Mann-Whitney U-test, ANOVA, Pearson's χ^2 test, Fisher's exact test, and nonparametric Kruskal–Wallis test by rank and median multiple comparisons were used depending on the type of analyzed data. Statistically significant predictors were identified by univariate logistic regression analysis. All reported *p*-values were based on two-tailed tests of significance; *p*-values < 0.05 were regarded as statistically significant.

To form comparable surgical groups of intervention and minimize the risk of bias, patients were selected using the propensity score matching (PSM) method. PSM statistical model included the gender, age, and type of AVM presentation, age at surgery, vascular territory, caliber of AVM vessels, size of feeding vessels, presence of fistulas and aneurysms, and Spetzler–Martin AVM grade.

Results

Baseline Characteristics of Study Groups

PSM enabled balancing the groups on baseline characteristics, which made the groups comparable not only in demographic indicators but also in disease severity, onset, and course as well as in AVM angiographic characteristics (►**Table 1**). The number of patients with a history of at least one AVM rupture was 27 (42.9%) in the embolization group and 31 (49.2%) in the MMT group ($p = 0.592$), with some patients presenting with a history of multiple bleeding episodes (6.35 and 12.7%, respectively, $p = 0.363$). Approximately 2/3 of patients in each group had AVM treatment initiated within the first three years after AVM symptom onset or MRI findings (65.1 and 68.25%, respectively, $p = 0.850$).

Approximately 2/3 of patients in each group had a complex vascular territory (69.8% and 68.3%, respectively, $p > 0.999$). The number of feeding arteries amenable to catheterization was 5 (3: 7) and 6.5 (4: 7), respectively, ($p = 0.313$), and the number of draining veins was 2 (1: 3) and 2 (1: 3), respectively, ($p = 0.093$).

Characterization of Treatment

Depending on the baseline patient's condition, AVM size, and characteristics, and by the principles of embolization, each patient underwent 1 to 11 successive stages of surgical treatment. ►**Figure 1** shows the overall study design and surgical options for enrolled patients. In the multimodal treatment group, the embolization series was followed by microsurgery in 30 (47.6%) patients, radiosurgery in 32 (50.8%) patients, and a combination of microsurgery and radiosurgery in 1 (1.6%) patient.

In total, patients of the EMB and MMT groups underwent 193 and 214 embolization stages, respectively, and 193 and 278 stages of all types of treatment. Most embolization stages were performed through the transarterial approach (177 (92.2%) and 202 (94.4%) stages, respectively, $p = 0.330$). The most common agents used for embolization were Onyx and its analogs (151 (78.6%) stages in the EMB group and 178 (83.2%) stages in the MMT group, $p = 0.210$); also, sulfacrylates (48 (25%) and 54 (25.2%), respectively, $p > 0.999$), coils (15 (7.8%) and 10 (4.7%), respectively, $p = 0.218$), PHIL (2 (1%) and 3 (1.4%), respectively, $p > 0.999$), and their combinations were used in one-stage procedures.

Efficacy of AVM Occlusion

After the last surgical stage, all patients underwent a follow-up examination at 6 and 12 months. The multimodal approach compared with monomodal embolization was slightly less effective regarding the number of patients with 100% occlusion immediately after treatment (30 (47.6%) vs 34 (54%), $p = 0.593$), but showed a significant advantage at the end of follow-up (59 (93.7%) vs 42 (66.7%), $p = 0.0002$). In this case, 3 (4.8%) patients in the EMB group had recanalization at the follow-up examination; there was no recanalization in patients of the MMT group ($p = 0.244$). The number of patients with subtotal occlusion ($\geq$ 90%) at the end of follow-up was 62 (98.4%) in the multimodal treatment group and 48 (76.2%) in the endovascular treatment group ($p < 0.001$). The median number of stages required for complete AVM occlusion, confirmed by follow-up angiography at 12 months after treatment, was 2 (2: 4) stages in the EMB group and 4 (3: 5) stages in the MMT group ($p = 0.310$).

Clinical Efficacy of Treatment

Both treatment approaches demonstrated a high clinical efficacy, with over 60% of patients lacking neurological symptoms at the end of follow-up. The key neurological outcomes of treatment and changes in the patient's condition at the end of follow-up are presented in ►**Table 2** and ►**Figure 2**. In this case, the MMT group showed better clinical outcomes in the number of patients with worsening of the baseline condition: 20 (31.7%) patients in the EMB group had worsening of the

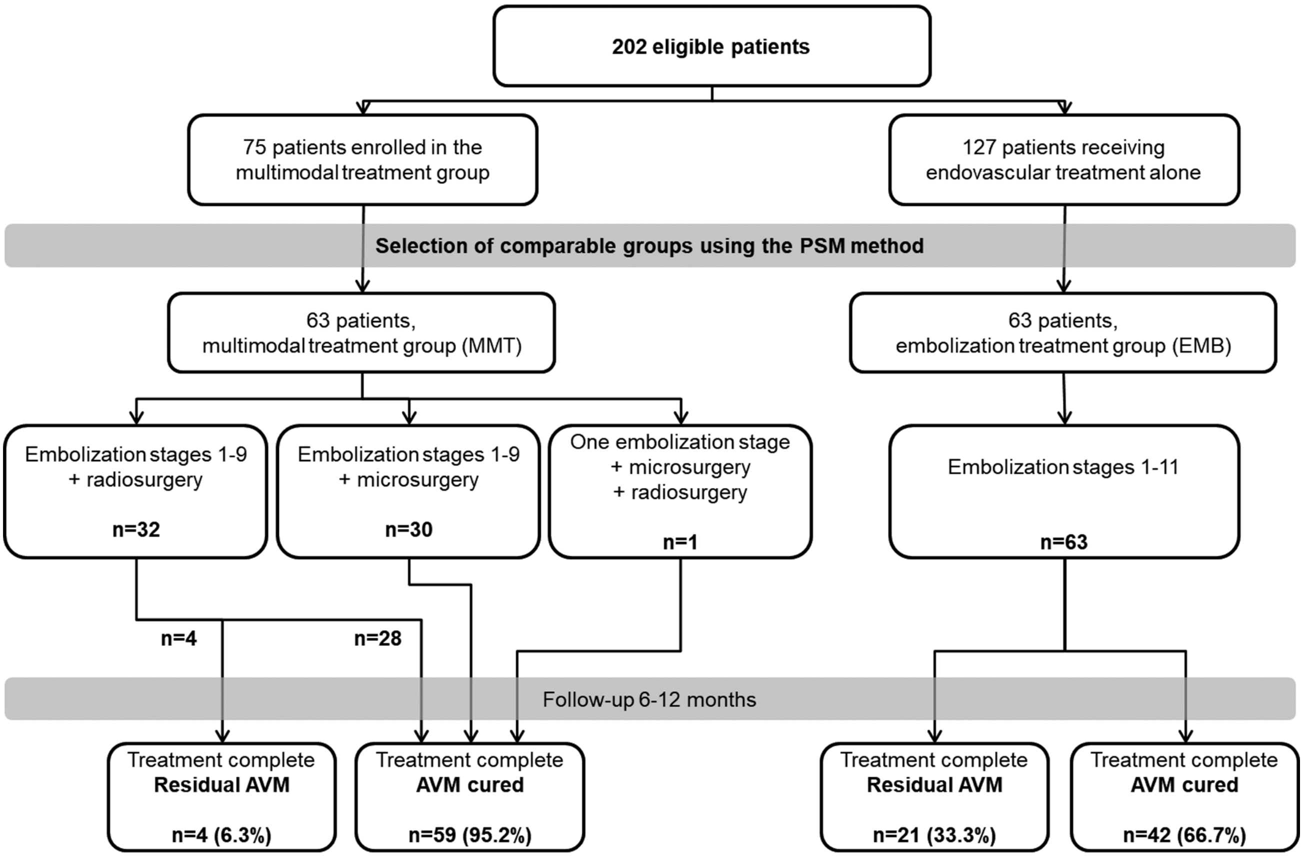

Fig. 1 Distribution of patients by surgical modality in the endovascular and multimodal treatment groups.

Table 2 Clinical outcomes in the compared groups

Clinical outcome	EMB (n = 63)	MMT (n = 63)	p value
Mortality	1 (1.6%)	0 (0%)	>0.999
Morbidity (the number of patients with mRS≥2 at the end of follow-up)	16 (25.4%)	8 (12.7%)	0.111
Full recovery of function (mRS = 0 at the end of follow-up)	39 (61.9%)	45 (71.4%)	0.349
Patients with a mRS score of 0–1 at the end of follow-up	45 (71.4%)	56 (88.9%)	**0.024**
Patients without worsening (preservation of mRS = 0 or any improvement in the condition)	39 (61.9%)	48 (76.2%)	0.123
Patients without improvement (retaining or worsening of preoperative deficit)	24 (38.1%)	15 (23.8%)	0.123
Patients with a decrease in the mRS by 1 or more points	20 (31.7%)	9 (14.3%)	**0.033**
Patients with a decrease in the mRS by 2 or more points	13 (20.6%)	3 (4.8%)	**0.015**

baseline condition by 1 or more mRS points compared with only 9 (14.3%) patients in the MMT group ($p = 0.033$); worsening by 2 or more points was detected in 13 (20.6%) and 3 (4.8%) patients, respectively ($p = 0.015$). A lethal outcome occurred in one patient of the EMB group, whereas there were no deaths in the MMT group ($p > 0.999$).

Perioperative Complications of Treatment

At each stage of the treatment, all technical complications, intraoperative bleeding, intraoperative thromboembolic complications, and any complications in the postoperative period were recorded. The groups demonstrated comparable results regarding the safety of surgery (►**Table 3**). Intraoperative complications at least at one stage occurred in 14 (22.2%) patients in the EMB group and 11 (17.5%) patients in the MMT group ($p = 0.656$); in this case, less than one-third of the complications led to persistent neurological deficit: 2 (3.2%) in the EMB group and 4 (6.3%) in the MMT group ($p = 0.680$). Postoperative complications at least at one stage occurred in 24 (38.1%) patients in the EMB group and 18 (28.6%) patients in the MMT group ($p = 0.345$); they led to persistent neurological deficit in 18 (28.6%) patients in the EMB group and 10 (15.9%) patients in the MMT group ($p = 0.133$). Endovascular treatment alone significantly

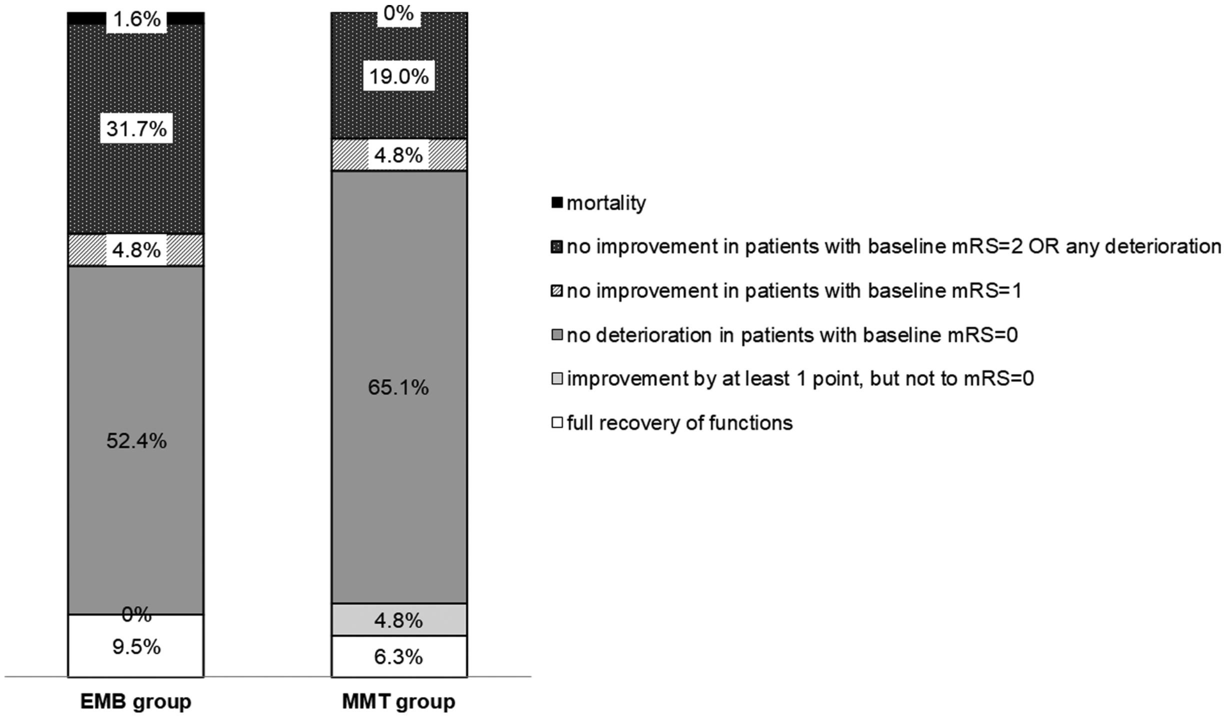

Fig. 2 Dynamics of neurological deficit in the compared groups.

Table 3 Intraoperative and postoperative complications in the groups

Complication	Number of patients		
	EMB (n = 63)	MMT (n = 63)	p value
Complications not associated with deterioration of the patient's condition			
Intraoperative complications			
Hemorrhagic	9 (14.3%)	9 (14.3%)	>0.999
Thromboembolic	5 (7.9%)	2 (3.2%)	0.273
Postoperative complications			
Hemorrhagic	13 (20.6%)	4 (6.3%)	**0.035**
Ischemic	11 (17.4%)	14 (22.2%)	0.656
Complications associated with deterioration of the patient's condition			
Intraoperative complications			
Hemorrhagic	1 (1.6%)	4 (6.3%)	0.365
Thromboembolic	1 (1.6%)	0 (0%)	>0.999
Postoperative complications			
Hemorrhagic	8 (12.7%)	1 (1.6%)	**0.033**
Ischemic	10 (15.9%)	9 (14.3%)	>0.999

increased the risk of postoperative hemorrhagic complications with a rate of 8 (12.7%) in the EMB group and 1 (1.6%) in the MMT group ($p = 0.033$). In this case, most of these complications of the endovascular approach occurred after one of the first 3 stages, whereas risks of postoperative bleeding upon multimodal treatment increased only after the 5th stage ($p = 0.011$). Emergent surgery due to a postoperative complication was required in 21 cases in 15 patients (23.9% of patients, 10.9% of stages) in the EMB group and 2 cases in 2 patients (3.2% of patients, 0.7% of stages) in the MMT group, ($p = 0.001$ for patients, $p < 0.001$ for stages).

Discussion

A comparison of two surgical strategies (endovascular embolization vs multimodal management) demonstrated that

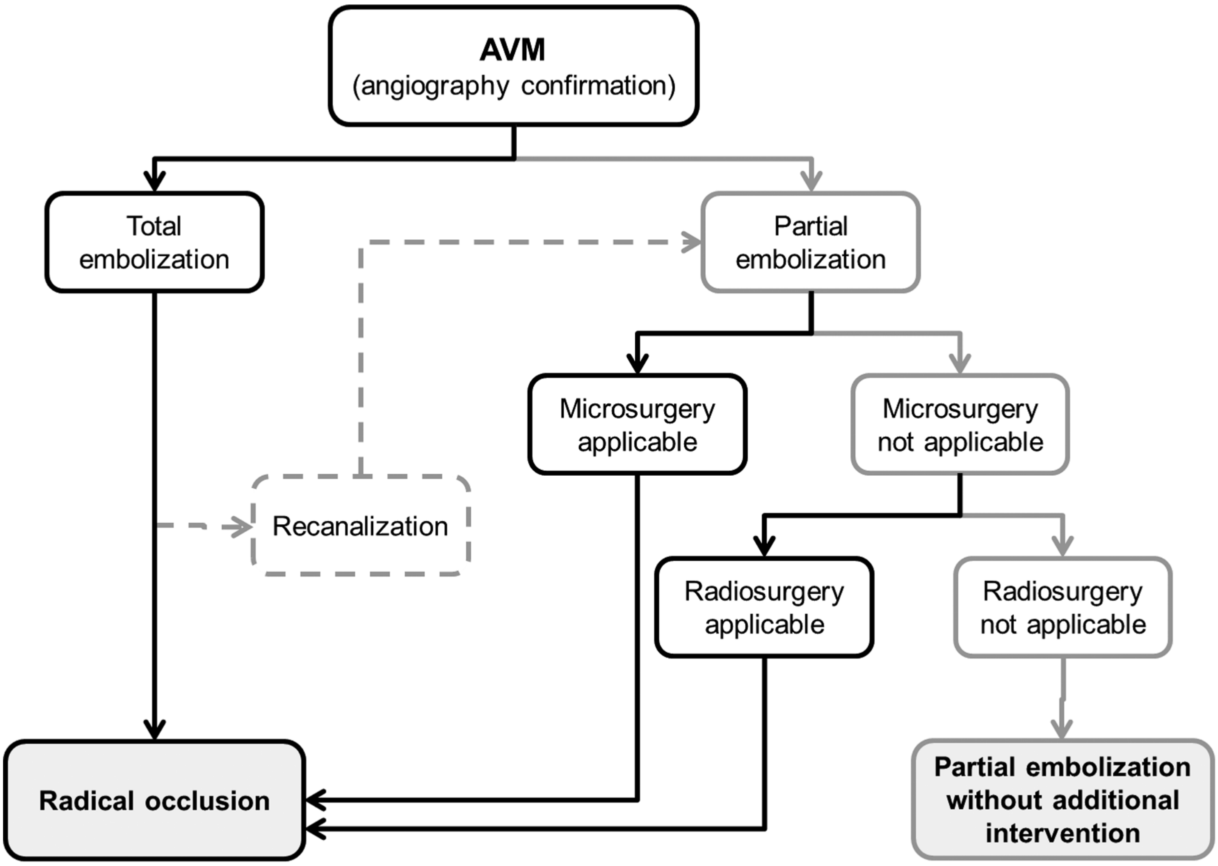

Fig. 3 Algorithm for multimodal AVM treatment.

embolization timely combined with other surgical options not only significantly enhanced the overall radicality of AVM treatment but also increased the safety of surgery and provided better clinical outcomes in patients. Comparison of clinical outcomes and dynamics of neurological deficit in patients after treatment showed that, in the groups comparable in baseline clinical conditions, the multimodal management provided complete AVM occlusion in 93.7% of patients and preserved or improved clinical parameters in a significantly larger number of patients compared with those in the group of endovascular treatment alone.

Because cerebral AVMs differ in size, location, and complexity of treatment, treatment methods also vary. To date, there are three AVM treatment modalities: microsurgery, endovascular embolization, and radiosurgery.[12] Each of them has its own advantages for certain subgroups of patients.[16] All of them are aimed at preventing hemorrhages, which require complete AVM occlusion.[23] At present, there is no ideal versatile treatment option, and their combination is optimal, depending on the patient characteristics and the AVM parameters, i.e. multimodal treatment. In this case, there are different approaches to multimodal treatment, which vary depending on the surgeon's preferences, current clinical guidelines, and protocols.[24,25] In some cases, microsurgery or radiosurgery can be the major option, with embolization being used only as a pretreatment stage to reduce the AVM size and mitigate the risks of the main surgical modality.[26,27] In other situations, embolization can be used as the main curative modality, switching to microsurgery or radiosurgery only if safe embolization of the malformation nidus is impossible.[21,27]

In this study, we demonstrated that the use of embolization alone, as the only surgical option, has high efficacy and safety rates comparable to data of other major centers.[15,28] However, the best angiographic and clinical results can be achieved if other treatment options may be timely supplemented, which allowed us to formulate a decision-making algorithm for multimodal AVM treatment (►**Fig. 3**). Endovascular embolization should be used as a curative option in strict accordance with the principles of safe embolization unless the risks of the next stage exceed the appropriate risks of microsurgery and radiosurgery. When achieving subtotal AVM occlusion, it is necessary to complete embolization; if the endovascular technique cannot provide complete AVM exclusion, microsurgical removal or radiosurgical treatment should be used as soon as possible. The latter is less preferable because of the delayed effect and should be considered on a residual basis.

An important factor affecting the choice of a treatment option is the degree of modality development in each medical center. Often, the authors focus on only one modality because they do not have the technical capacity or sufficient experience to implement other intervention types. This limits the surgical approach and prevents the surgeon from switching to another type of intervention to reduce the risk of complications and leads to unsatisfactory treatment outcomes. In this study, we demonstrated that the use of one modality alone significantly increased the risks of short-term and long-term treatment complications associated with the deterioration of the patient's condition. For this reason, clinical efficacy indicators in the group of embolization alone were comparable to those in the ARUBA study.[10] However, the addition of microsurgical and radiosurgical modalities reduces the number of postoperative complications associated with the development or worsening of neurological deficit in patients and increases the number of patients with an mRS score of 0–1 to 88.9% at the end of follow-up. This result is comparable to 87.1% obtained in one of the largest studies in 142 ARUBA-eligible patients who underwent multimodal treatment[15] and demonstrates a significant expansion of the opportunities for surgical treatment if the surgeon has the technical capability and experience in using different modalities.

Until now, the unresolved issue of surgical management of AVMs is the need for intervention, and disputes about whether AVM removal reduces the risks of a natural course do not subside. The most famous study that aimed to answer this question, ARUBA,[29] was prematurely terminated; later, its results received much criticism.[14,30] In the present study, we showed that the use of even one modality in modern conditions provided total occlusion in 66.7% of patients (which is significantly higher compared with 44.3% in ARUBA, $p = 0.007$) without deterioration of the health condition in 58.4% of patients; addition of other surgical options increases these indicators to 93.7% and 78.1%, respectively, which is significantly higher than those demonstrated in ARUBA and is comparable with data from other studies conducted in comparable groups of patients.[1,12,15,19,25]

This study has some limitations. First, the impossibility of ethical and legal reasons to organize a randomized prospective study led to the need to use the PSM method to eliminate the potential selection error, which, nevertheless, allowed the selection of comparable groups. Another limitation was exclusion of patients with 100% one-stage embolization because this option is valid only for Spitzler–Martin grades I–II malformations without additional hemodynamically significant features and small deeply located class B AVMs and is not suitable either for staged embolization or for multimodal management. The last limitation was the small size of each group, which prevented separate evaluation of patients with and without rupture history without a significant loss of study power but enabled the identification of some statistically significant differences between the approaches used.

Conclusions

Curative embolization should be considered as the main option of the multimodal algorithm and supplemented, if necessary, with radiosurgery and microsurgery. The technical capability and surgeon's experience, which enable the use of all three modalities and their combinations, can significantly increase the radicality of AVM cure and enhance treatment safety, even in patients with rupture history or preoperative neurological deficit.

Authors' Contribution
All authors contributed equally to this work.

Disclosure of Funding
None.

Conflicts of Interest
The authors have no conflicts of interest to declare.

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