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Combined Treatment of Cerebral Arteriovenous Malformations. Experience of the Burdenko Neurosurgical Institute

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Objective. Despite the achievements of recent years, cerebral arteriovenous malformations (AVMs) remain a challenge to treatment. The objective of this study was to develop the recommendations for combined treatment of AVMs that is based on analysis of the available material and published data. **Material and Methods.** The study included 93 patients hospitalized at the Neurosurgical Institute for combined treatment of cerebral AVMs in 2010—2014. A group of combined surgery (resection of an AVM with preoperative embolization) consisted of 40 patients, and a group of combined radiotherapy (irradiation after partial embolization or partial resection of an AVM) included 53 patients. Thirty-six patients underwent radiosurgery, and 17 patients received stereotactic radiation therapy. Both groups were analyzed in terms of outcomes, complications, and follow-up results. **Results.** In the group of combined surgery, according to the Glasgow Outcome Scale, good outcomes (score of 4 or 5) were achieved in 35 (87.5%) patients at discharge and in 27 (90%) patients during follow-up. Treatment outcomes, surgery duration, and the amount of blood loss were not significantly different from those in the control group. Complete AVM obliteration was achieved in 29 (80.6%) patients 3 years after radiosurgery and in 8 (47%) patients after stereotactic radiation therapy. In discussion, these findings are compared to the published data, and recommendations for AVM treatment are suggested. **Conclusion.** The combined treatment of AVMs is an effective therapeutic approach for patients with complex AVMs (Spetzler—Martin grade III—IV AVMs). Successful treatment of AVMs requires careful planning and teamwork of vascular and endovascular neurosurgeons, radiologists, and neurologists.

Keywords: *arteriovenous malformation, combined treatment, surgical treatment of AVM, preoperative embolization, radiosurgery, stereotactic radiation therapy.*

List of abbreviations

AVM — arteriovenous malformation;

GOS — the Glasgow Outcome Scale;

H&E — hematoxylin and eosin staining;

MSCT/MRI — multislice computed tomography/magnetic resonance imaging;

NBCA — n-Butyl cyanoacrylate;

PCA — posterior cerebral artery;

PCF — posterior cranial fossa;

RS — radiosurgery;

SRT — stereotactic radiation therapy;

TBD — total boost dose.

Arteriovenous malformation (AVM) is a congenital malformation of blood vessels, which was first described by W. Hunter in 1764 [1]. The incidence of AVMs in the population is 1.34 per 100,000 with male:female ratio of 1.1:1 (males are slightly predominant) [2, 3]. About 50% of AVMs are manifested with intracranial hemorrhage followed by the development of persistent neurological deficit in 21—83% of patients. The risk of repetitive hemorrhage is 6—17%; mortality rate is 10—15% [4].

Every year, approximately 120 patients with cerebral AVMs are admitted for surgery to the Burdenko Neurosurgical Institute. The choice of treatment is often a subject for discussion with the allowance for changing views to AVM surgery and accumulation of data on radiosurgeries. Combined treatment of AVMs (two or more techniques used in the treatment) did not include system analysis for a long time, while the role of the latter is becoming increasingly significant. In this study, a team of specialists of the Burdenko Neurosurgical Institute presents both an analysis of the outcomes of combined treatment for patients with AVMs and the views on therapeutic approaches for the disease.

Material and Methods

The study included 93 patients admitted to the Burdenko Neurosurgical Institute for the combined

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treatment of cerebral AVMs in 2010—2014. Retrospective analysis included 40 patients of "surgical" group who underwent embolization and resection of an AVM and 53 patients of "irradiation" group who underwent stereotactic radiation therapy (SRT) after either partial embolization or subtotal resection of an AVM.

I. AVM resection combined with preoperative embolization

The group included 40 patients with AVMs of the cerebral hemispheres or the posterior cranial fossa (PCF). The mean age of patients was 32.1±12.9 years. Male:female ratio was 26:17. Treatment outcomes in this group were compared to those of the control group to evaluate the effectiveness of preoperative embolization and its impact on treatment outcomes, intraoperative blood loss, surgery duration, time of stay at hospital, and other side effects of treatment. The control group was selected randomly among patients with AVMs who were operated on in 2010—2013 but did not undergo preoperative embolization. No statistically significant changes in the number of patients, age, sex, and clinical manifestations of the disease were revealed in the control croup as compared to the study group ($p<0.05$). AVMs were preoperatively evaluated using the Spetzler-Martin AVM grading system with the allowance for the state of the critical regions of the brain: language zone, visual cortex, sensorimotor area, the area of the internal capsule, subcortical nuclei, and deep cerebellar nuclei.

More data on the study and control groups are presented in **Table 1**.

Distribution of AVMs in the study and control groups with respect to localization is presented in **Table 2**.

The study group included both patients who underwent AVM embolization and resection at the Burdenko Neurosurgical Institute within one day (33 patients) and patients with partially embolized AVMs who were admitted for AMV resection from other hospitals (7). The preoperative embolization was aimed at occlusion of difficult-to-access and deep-seated afferents of AVMs and hemodynamic aneurysms.

The degree of AVM embolization was evaluated based on angiograms in two projections according to the extent of contrasted areas and the rate of blood bypass in a malformation as a percent of the basic data. Functional treatment outcomes were evaluated on the Glasgow Outcome Scale (GOS). The follow-up data were obtained during control examinations of patients in the department or via a telephone interview. The duration of AVM resection, intraoperative blood loss, time of stay at hospital (including the time at the intensive care unit), as well as costs for each type of treatment were analyzed to assess the effectiveness of AVM embolization. Performance work and social rehabilitation of patients were also analyzed during follow-up examinations.

Outcomes of AVM resection combined with preoperative embolization

Thirty-nine (97.5%) out of 40 patients underwent embolization and resection of an AVM; one patient died due to complications after endovascular surgery.

AVM embolization was performed using microcoils (9 patients), Histoacryl (8), microemboli (2), NBCA (15), and Onyx (3); combinations of the aforementioned embolic agents were used for 3 patients. Three patients with an aneurysm in the posterior inferior cerebellar artery and 1 patient with an aneurysm in the posterior cerebral artery (PCA) underwent microcoil endovascular occlusion of a hemodynamic aneurysm. Preoperative embolization was performed at 20—90% of the initial AVM volume. More than 50% of the AVM nidus was occluded in 29 (72.5%) patients; of them, 5 patients (12.5%) underwent subtotal embolization **(Fig. 1)**.

In the total of 39 patients, AVM were successfully resected via microsurgery. In the early postoperative period, complete AVM resection during the combined treatment was confirmed for 23 patients based on the selective angiography data and for 3 patients based on the MSCT angiography data; the completeness of AMV resection for other patients was confirmed on the basis of the MSCT/MR angiography data in the late postoperative period.

Good outcomes (GOS score of 4 or 5) were obtained in 35 (87.5%) out of 39 patients in the group of combined treatment and in 37 (92.5%) patients of the control group. Poor outcomes (GOS score of 3) were detected in 3 patients after combined treatment and in 2 patients of the control group. One patient died in each group. In the study group, the patient died due to migration of a glue into the draining vein and superior sagittal sinus, which was followed by the development of diffuse edema and brain herniation. In the control group, the patient with an AVM in the PCF died due to massive air embolism. No statistically significant changes were observed in the treatment outcomes of both the study and control groups (U-test, $p>0.05$).

Long-term outcomes were assessed in 30 (75%) out of 39 operated on patients. The mean follow-up period was 27.6 months. According to the follow-up data, good treatment outcomes (GOS score of 4 or 5) were achieved in 27 (90%) patients; one patient remained severely disabled (GOS score of 3). Two patients died due to causes not related to their surgeries. Functional treatment outcomes of the study and control groups on the GOS scale are summarized in **Table 3**.

The average length of stay at hospital and in the intensive care unit of patients who underwent combined treatment was slightly longer compared to the control group. This fact can be explained by multistage surgeries requiring teamwork of two surgical teams and by postoperative monitoring of a number of parameters for

Table 1. **Characteristics of the study and control groups**

Characteristics	Study group (embolization + resection)	Control group (resection)
Mean age of patients (σ), years	32,1±12,9	30.47±11.1
Male:female ratio	24:16	25:15
Critical region	26	23
Hemorrhage in past medical history, number of patients	23	27
Spetzler-Martin AVM grading system, number of patients		
I	2	8
II	17	28
III	18	4
IV	3	–
V	–	–
Total	40	40

Table 2. **Characteristics of the study and control groups with regard to AVM localization**

Localization	Study group (embolization + resection)	Control group (resection)
Temporal lobe	10	11
Temporo-occipital region	3	1
Occipital lobe	13	9
Frontal lobe	5	9
Parietal lobe	1	5
Parieto-occipital region	4	2
PCF	4	3
Total	40	40

preventing the syndrome of hyperperfusion and other complications.

No statistically significant changes were observed in the study and control groups regarding mean time of surgery and blood loss exceeding normal values of 500 mL (U-test, p>0.05).

Preoperative embolization required on average RUR 247,859; direct microsurgical intervention costed RUR 150,000—195,000, depending on the complexity of surgical procedures. Combined treatment required on average RUR 403,484. (All these prices are valid for October, 2014).

Duration of surgery, costs, and abnormal (regarding mean values) blood loss during the treatment are summarized in **Table 4**.

Case report 1

A 22-year-old male patient *B.* presented with the diagnosis of an AVM in the left cerebellar hemisphere. The patient underwent 17 Onyx glue embolization of the difficult-to-access pole of the AVM, which was followed by AVM resection.

Three months after the treatment, the patient was examined after severe intraparenchymal hemorrhage with fourth ventricle occlusion. Angiography data revealed an AVM in the left cerebellar hemisphere, which was feeding generally from hypertrophied anterior inferior and posterior inferior cerebellar arteries on the left. Blood outflow followed the convoluted drainage vein towards the confluence of sinuses. Considering the blood supply of the AVM from a difficult-to-access afferent vessel of the anterior inferior cerebellar artery circulation, Onyx partial embolization of the oral region of the AVM nidus was the first stage of the surgery: about 50% of the initial contrasted volume of the malformation was occluded. The AVM was completely resected during the subsequent direct surgery. The border zone of the embolized malformation was well differentiated from brain tissue, and AVM resection through the perifocal area was followed by a slight hemorrhage. The postoperative period proceeded relatively well, and the patient was discharged in satisfactory condition with the absence of neurological deficit **(Fig. 2)**.

Case report 2

A 36-years-old male patient *G.* was admitted with a diagnosis of an AVM in the left parietal parasagittal region. The patient underwent partial embolization using Histoacryl and resection of the AVM.

Three times the patient suffered hemorrhage from the AVM of parietal region on the left (the central gyrus region). The patient underwent two times AVM embolization using Histoacryl at the place of residence. He suffered from partial epileptic seizures in the form of tonic seizures in his right upper limb, sometimes from generalized seizures. Neurological status at admission revealed the absence of focal neurological symptoms. Angiography data revealed the contrasted area of an AVM in the parietal parasagittal region that reached 30% of the original volume (**Fig. 3a—d**).

AVM resection through the perifocal area was almost bloodless. Vessels embolized by Histoacryl were grayish-

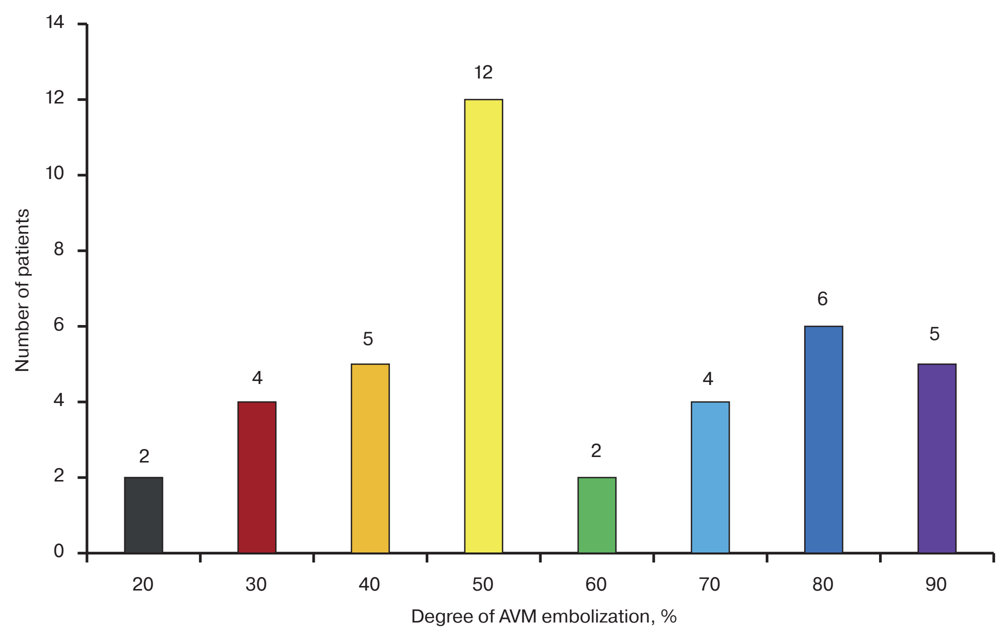

Fig. 1. **The degree of preoperative AVM embolization.**

Table 3. **The outcomes of treatment on the Glasgow Outcome Scale in the group of combined treatment and control group**

Glasgow Outcome Scale	Combined treatment. Outcomes at discharge	Delayed outcomes	Control group
5	12	15	18
4	23	12	19
3	3	1	–
2	—	—	2
1	1	2	1
Total	39	30	40

Table 4. **Treatment time, blood loss, duration and costs of surgeries in the study and control groups**

Index	Combination therapy	Control group
Average length of stay at hospital, bed-days	21.5	16.6
Average length of stay in the intensive care unit, bed-days	2.4	0.9
Average length of stay prior to surgery, bed-days	6.9	6.1
Average length of stay after surgery, bed-days	14.4	10
Blood loss of more than 500 mL, patients	5	7
Average duration of the surgery, h	4.1	3,9
Average cost of treatment, RUR	403 484	155 625

colored and had dense structure and areas in the border zone of the AVM with continued blood flow; these vessels were occluded with difficulty. As an outcome of the surgery, the AVM was resected completely, which was confirmed by angiography (**see Fig. 3e**). Microscopy revealed a mass of Histoacryl visualized in the vessel lumen and perivascular lymphocytic infiltrate in the vessel wall, which were caused by embolization (**see Fig. 3f**).

The patient was discharged with the absence of neurological deficit. No epileptic seizures were observed during the 2-year follow-up. The patient works and is completely socially adapted.

II. Stereotactic irradiation after AVM embolization or incomplete AVM resection

The group included 53 patients with cerebral AVMs, who underwent stereotactic irradiation after surgery or embolization in 2010—2011. Prior to scheduling radiation therapy, patients were counseled by vascular neurosurgeons: no surgical treatment was indicated for

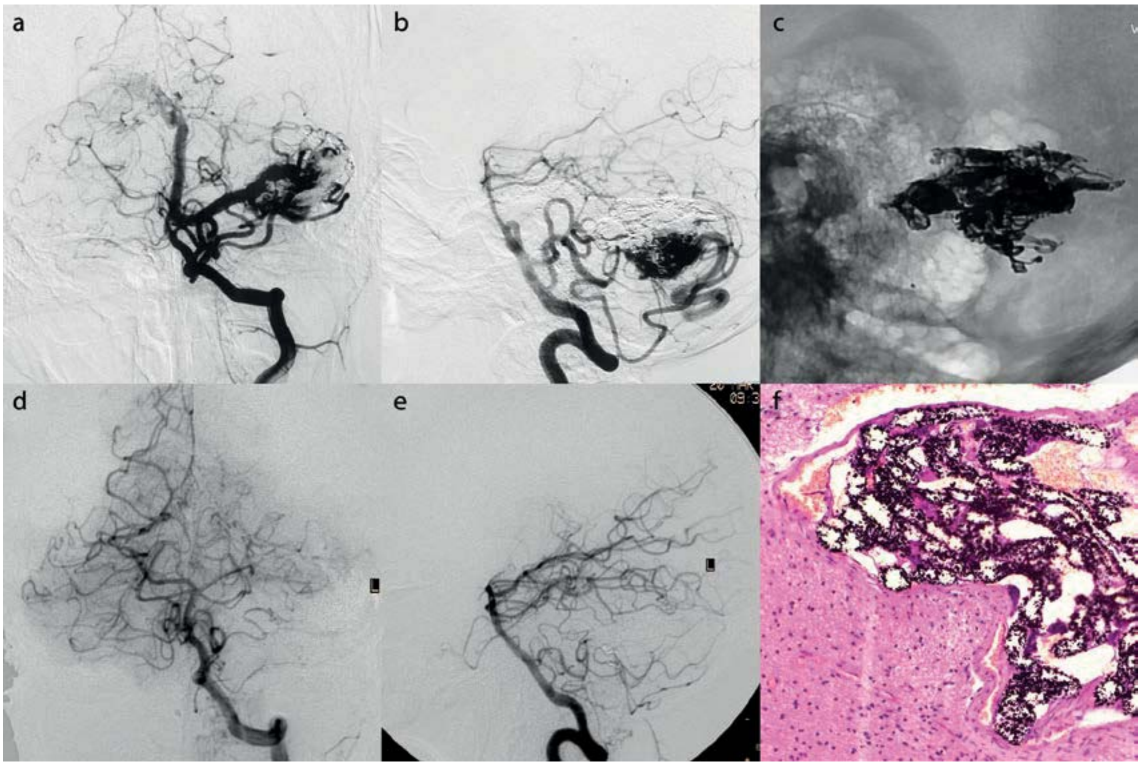

***Fig. 2.* Patient *B.* (case report 1). Embolization and resection of the AVM in the left cerebellar hemisphere.**

a—e — selective left-sided vertebral angiography; a, c — in frontal and lateral views, about 50% of the initial AVM volume is contrasted after Onyx embolization; d, e — no data on residual AVM was confirmed based on control angiography; f — Onyx mass is seen in the lumen of the vessel during microscopy of the specimen (× 200, H&E).

all candidates. The inclusion criterion in the study was the 3-year follow-up after irradiation and the outcome of radiation therapy confirmed with the MR/CT angiography data. Radiosurgery (RS) included stereotactic irradiation of a target in a single fraction and SRT in 2—5 fractions with target variables (**Table 5**).

Forty-three patients after partial endovascular embolization of an AVM, 8 patients after incomplete AVM resection, and 2 patients after endovascular and microsurgical treatment were subjected to stereotactic radiotherapy. A detailed description of the study group and the distribution of patients according to the Spetzler-Martin AVM grading system and clinical manifestations of the disease are presented in **Table 6**.

In terms of surgery, patients subjected to stereotactic irradiation were referred as a complex group of high risk. In almost half of all patients (25 patients, 47.2%), an AVM was referred as the Spetzler-Martin grade III malformation; in 19 (35%) patients, an AVM was referred as grade IV—V. The majority of patients (41 cases) had previously experienced hemorrhage from an AVM, 9 patients had suffered from epileptic seizures, and an AVM had manifested with headaches and other pseudotumor symptoms in 3 patients **(see Table 6**). More than half of the study population (32 patients) included patients with hemispheric AVMs. Thirteen patients with deep-seated subcortical AVMs, 2 patients with intraventricular AVMs, and 3 patients with an AVM of a hemisphere or of the cerebellar vermis were irradiated. Distribution of patients with regard to AVM localization is presented in **Table 7**.

Eight patients underwent SRT using the CyberKnife and 9 patients using the Novalis device. Both groups were subjected to irradiation in the hypofractionated regimen with the total boost dose (TBD) of 24—27 Gy on the CyberKnife (2 fractions) or TBD of 35 Gy on the Novalis (5 fractions), respectively.

The dose of irradiation depended on the location and extent of an AVM, estimated radioreactions, preexisting neurological deficit, and the fact of hemorrhage in the past medical history. Depending on the system used for irradiation, the isodose level typically ranged from 50 to 70% in the case of Gamma Knife irradiation and from 75 to 95% in the case of irradiation using linear electron accelerators. As the medication assistance, all patients received a single dose of dexamethasone (8 mg) at the end of radiosurgical procedure. Administration of other medications (e.g., anticonvulsants, cardiac medications, painkillers, etc.) continued.

For radioreaction assessment after SRT, the patients underwent MRI of the brain after 6 months and then after 1 and 2 years, depending on the severity of radiation-induced edema, radiation necrosis, and other

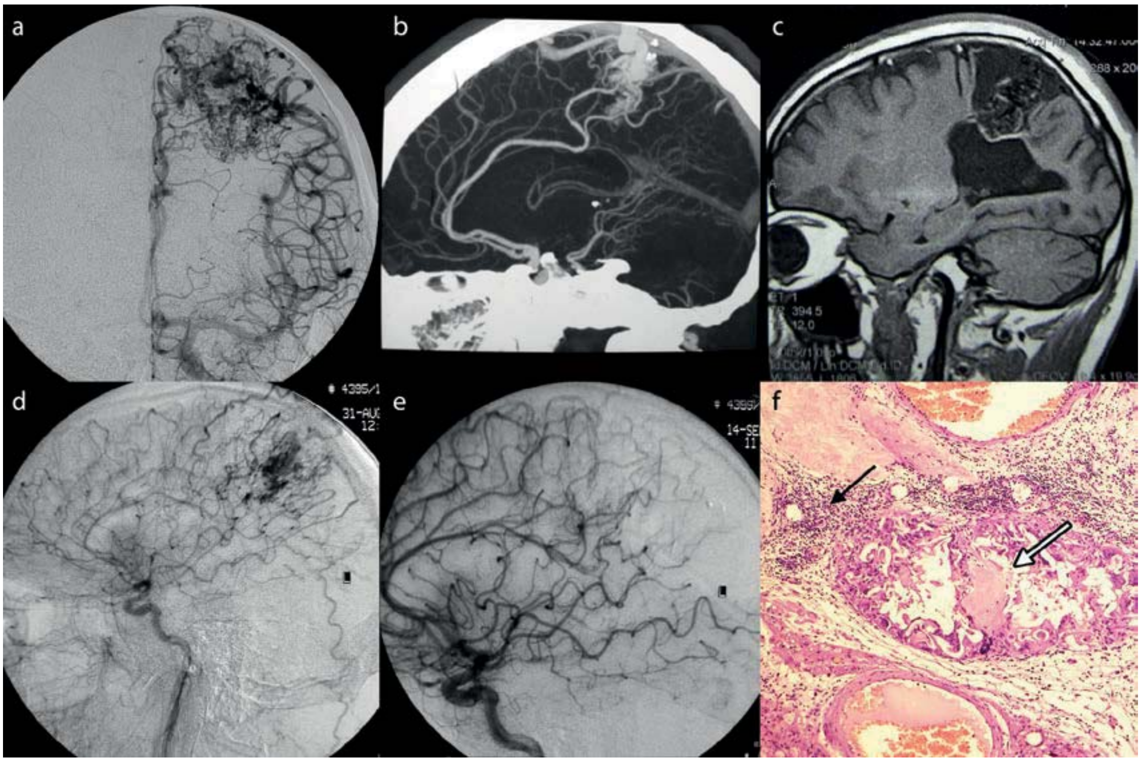

Fig. 3. **Patient *G.* (case report 2). Resection of the previously embolized AVM in the parietal lobe.**

a—c — AVM and posthemorrhagic changes in the brain are visualized with left-sided carotid angiography, MSCT angiography, and MSCT; d — AVM after partial Histoacryl embolization and resection (e); accumulation of Histoacryl (white arrow) and perivascular infiltration of the vessel wall (black arrow) are seen microscopically; × 200, H&E.

complications. Obliteration of an AVM was evaluated based on the selective angiography and MR/MSCT angiography data 3 years after irradiation. The results of control examinations were studied by a council of three specialists (radiation therapist, radiologist, and neurosurgeon). In the case of doubtful or incomplete data, the patients were subjected to control selective angiography. If functioning fragments of an AVM were detected after 3 years, the patients were recommended to undergo repeated SRT. In the case of a significant decrease in the AVM volume (more than 70%) after 3 years and no hemorrhage in the latent period, the patients were recommended to undergo repeated angiography after 2 years.

Performance status of patients after radiation therapy was evaluated on the Karnofsky scale.

II. The outcomes of radiation therapy for AVM after embolization or incomplete resection

Radiosurgery. The mean follow-up period was 3.14±0.61 years. The mean volume of irradiated AVM was 12.24 (range of 8—36) cm^3. The outcomes of radiosurgical irradiation were confirmed according to the selective angiography data in 19 (36%) patients and MSCT/MR angiography in 34 (64%) patients.

Complete AVM obliteration after radiosurgical treatment was achieved in 29 (80.6%) patients (i.e., in 9 patients after Gamma Knife irradiation, in 15 patients after the Novalis, and in 7 patients after CyberKnife treatment). RS caused partial obliteration of an AVM in 4 (11%) patients and proved to be ineffective in 3 patients. The outcomes of RS are summarized in detail in **Table 8**.

Symptomatic radiation-induced responses (edema accompanied by neurological symptoms), radiation necrosis, and cysts were observed in 1 or 2 (11—14%) patients who underwent different types of irradiation. Repetitive hemorrhage during the 3-year period of follow-up occurred in 1 patient after irradiation using the Gamma Knife and in 1 patient with a large AVM after Novalis treatment. As a result, 1 patient died from a hemorrhage. Thus, the overall mortality rate was 1.8%. The positive effect on the epilepsy syndrome (reduction

Table 5. **Distribution of patients with regard to the type of radiation therapy**

Type of treatment	Novalis	CyberKnife	Gamma Knife	Total
Radiosurgery	18	7	11	36
Stereotactic radiation therapy	9	8	–	17
Total	27	15	11	53

Table 6. **Characteristics of patients with cerebral AVMs who underwent stereotactic irradiation**

Characteristics	Number of patients
Total number of patients	53
Male:female ratio	24:29
Mean age of patients (σ), years	33.4±36.7
Gamma Knife	11
Novalis	27
CyberKnife	15
Grade according to the Spetzler-Martin AVM grading system	
I	2
II	7
III	25
IV	11
V	8
Main clinical syndrome	
Hemorrhage	41
Epilepsy syndrome	9
Pseudotumor symptoms	3
Previous treatment	
AVM embolization	43
Incomplete AVM resection	8
Embolization + resection	2

Table 7. **Distribution of patients with AVMs who underwent radiation therapy with regard to AVM localization**

AVM localization	Number of patients
Cerebral hemispheres	32
Corpus callosum	2
Thalamus/basal ganglia	13
Pineal region	1
Ventricle	2
Cerebellum	3
Total	53

in seizure frequency, reduced doses of anticonvulsants, and changes in the severity of attacks towards milder episodes) was detected in half of the patients in each subgroup. Improved performance status on the Karnofsky scale was observed in approximately one-third of the patients, regardless of the device used, which was likely associated rather with the natural recovery of neurological function after hemorrhage than with the specific impact of irradiation. Due to a small patient selection, it was not possible to achieve a statistically significant data on the role of radiation therapy in terms of functional outcomes and epilepsy syndrome.

Stereotactic radiation therapy. SRT outcomes in 17 patients with confirmed 3-year-follow-up data are presented in **Table 9**. A small number of patients in the groups did not allow us to carry out valid statistical processing of the data. However, it was clear that the efficacy of SRT was lower (~50%) compared to the outcomes of AVM obliteration, and complication rates were higher than those of RS.

Case report 3

A 32-year-old female patient *Sh.* was admitted with the diagnosis of an AVM in the left occipital lobe. The treatment included Histoacryl embolization (2005), Onyx embolization (2006), RS using Novalis (2008), and AVM resection (2011).

Past medical history of the patient revealed that she had suffered from headaches for a long time and the attacks became more frequent after childbirth. An AVM in the left occipital lobe was detected based on MRI of the brain. According to angiography data, the AVM received blood supply from the branches of the left posterior and medial cerebral arteries; the blood was drained into the left transverse sinus (**Fig. 4a, b).** During two endovascular surgeries in 2005 and 2006, the AVM was embolized approximately on two thirds of the contrasted volume (**see Fig. 4c**). In 2008, due to recanalization of the malformation, AVM embolization using Onyx was performed (**see Fig. 4d**); the patient refused proposed AVM resection. It was decided to irradiate the residual portion of the malformation using the Novalis system. The target volume was 1.47 cm^3; the isocenter dose of 26 Gy was delivered with 80% isodose (**see Fig. 4e**). However, a contrasted area of a small residual portion of the AVM was still detected during control angiography after 2.5 years. The AVM was successfully resected, which was confirmed with the MSCT angiography data after 1 year. The patient was neurologically preserved except visual field defects (complete right-sided hemianopsia).

Case report 4

A 31-year-old male patient *A.* was admitted with the diagnosis of an AVM in the right temporal lobe. The treatment included clipping of afferent vessels (1997), proton therapy (2000), embolization using TRUFILL microcoils (2004), and RS with the Novalis device (2008).

As a child, the patient experienced two times severe parenchymal hemorrhage from the AVM in the right temporal lobe; both times the patient underwent emergency surgery at the place of residence. During reoperation in 1997, AVM afferents from the right medial cerebral artery were clipped after hematoma resection. In 2000, proton therapy was performed with no evidence of a positive effect: the AVM continued to receive blood supply from the branches of the left medial cerebral artery and meningeal branches of the external carotid artery (**Fig. 5a**). At the Burdenko Neurosurgical Institute, endovascular AVM management using TRUFILL microcoils was performed in 2004, and the residual portion of the AVM was irradiated using the Novalis system in 2008. The target volume was 4.85 cm^3; the isocenter dose of 26 Gy was delivered with 80% isodose

Table 8. **Treatment outcomes, epilepsy syndrome dynamics, and complications after radiosurgery with regard to the number of patients**

Characteristics/goal	Novalis	CyberKnife	Gamma Knife
Total number of patients	18	7	11
Total obliteration	15	5	9
Partial obliteration	2	1	1
No obliteration	1	1	1
Improvement of neurological status (on the Karnofsky scale)	6	2	3
Epilepsy syndrome dynamics			
Improvement	2 out of 4	1 out of 2	2 out of 4
Epilepsy seizures after treatment	—	1	—
Complications			
Symptomatic radioreactions	2	1	1
Radiation necrosis	1	—	1
Repetitive hemorrhage	1	—	—
Cysts	1	—	1
Mortality	1	—	—

Table 9. **Treatment outcomes and complications after SRT for partially embolized or resected AVMs with regard to the number of patients**

Outcome	Novalis	CyberKnife
Total	9	8
Total obliteration	4	4
Partial obliteration	2	2
No obliteration	3	2
Symptomatic edema	2	2
Radiation necrosis	2	1

(see Fig. 5b, c). Control selective angiography after 6 years revealed the absence of contrasted AVM mass. No focal neurological symptoms were detected.

Discussion

In terms of surgical treatment and its risks, patients with cerebral AVMs are a sufficiently diverse group. The Spetzler-Martin AVM grading system (1986) has proven particularly useful to assess the risk of AVM treatment. This scale still remains the most accurate integrated scale for predicting the outcomes of surgical treatment. For instance, the surgery of grade I—III AVMs is being at moderate risk, while grade IV—V AVMs involve high risk of postoperative complications and mortality. The therapeutic approach for grade I—II AVMs is generally doubtless, but grade III—IV AVMs (which are large in size, have deep-seated afferents, the presence of drainage, and often involve the critical regions of the brain) are a complex subject for treatment.

Our study demonstrated that preoperative embolization of the portions of a malformation that are difficult to access and deep-seated afferents enables switching an AVM to the group at lower risk without impairing treatment outcomes. For example, 21 patients with Spetzler-Martin grade III—IV AVMs were operated on in the study group, while only 4 patients of the same grade underwent surgery in the control group; good treatment outcomes (early and delayed) were achieved in both groups.

The role of endovascular treatment of AVMs has somewhat changed in recent years. The literature analysis shows that total occlusion can be achieved in 16—32.8% of cases; however, some authors who are using Onyx give higher rates of total AVM embolization (51%). According to I. Saatci et al. [5], the risks of endovascular embolization of AVMs (2—8.7%) and mortality rate (0.8—3%) are sufficiently low (**Table 10**).

It should be noted that the reliability of endovascular treatment is lower compared to microsurgical treatment. This is due to delayed recanalization of a malformation and opening of new perinidal vessels around the nidus, which is detected in 15—20% of cases (J. Mathis et al. [11]). Histoacryl embolization of AVMs shows signs of recanalization within 6—12 months. As a primary treatment, AVM embolization is justified for small lobar AVMs with afferents easily accessible for cannulation and with the best prospect of complete embolization. In other cases, endovascular treatment should be regarded as a supplementary option but not as an independent treatment mode for AVMs.

The role of embolization of an AVM before resection and RS is slightly different with respect to the purposes of preoperative preparation:

(1) cutting off deep-seated inaccessible for direct surgery afferents from circulation of the choroidal arteries, from PCA, and from perforating arteries;

(2) decreased volume of the functioning nidus;

(3) decreased rate of shunting of blood in an AVM;

(4) occlusion of hemodynamic aneurysms.

When performing preoperative AVM embolization, the specialists of the Burdenko Neurosurgical Institute follow the established surgical principles:

1. High-flux AVM afferents should be occluded with microcoils, since the use of a glue bears the risk of distal migration of a glue followed by drainage occlusion of an AVM and sinus occlusion.

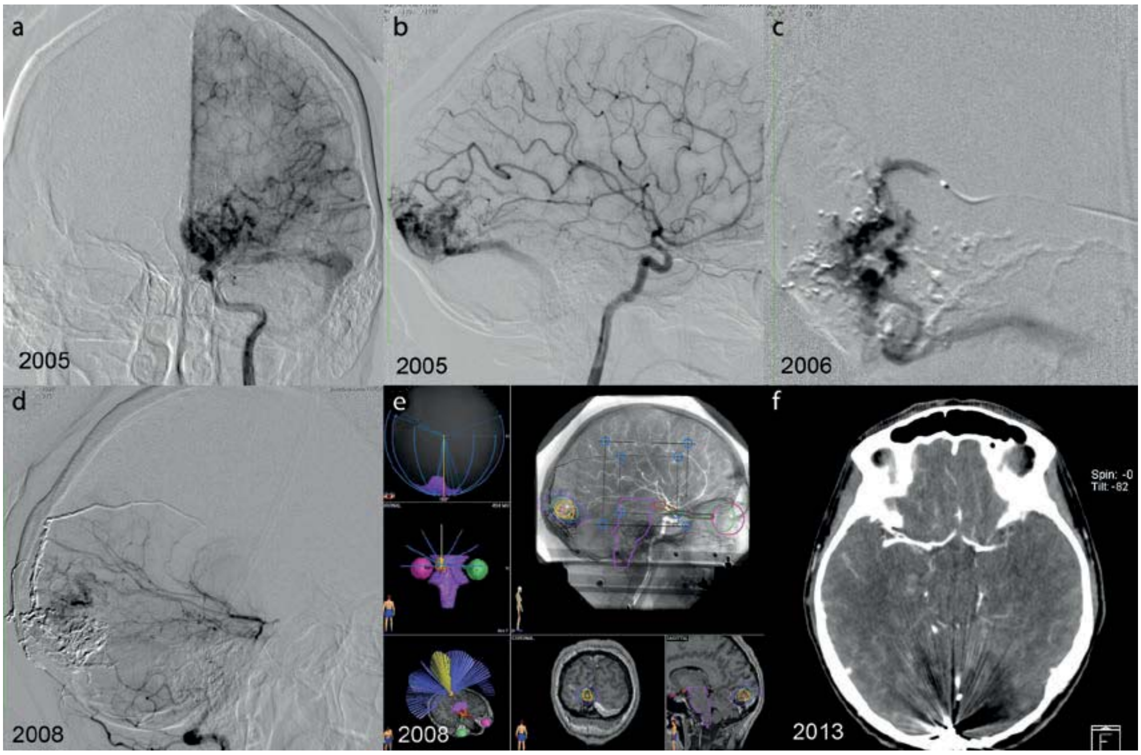

Fig. 4. **Patient *Sh.* AVM in the left occipital lobe.**

a, b — left-sided carotid angiography reveals a contrasted area of an AVM; AVM embolization using Histoacryl in 2006 (c) and Onyx in 2008 (d) are seen on intraoperative vertebral angiograms; e — scheduling RS using the Novalis system; f — control MSCT angiography 1 year after AVM resection: a postoperative cyst is visualized in the area of the resected malformation; in the angiography mode, no data on a residual AVM were detected.

2. Obliteration of AVM stroma is not an absolute goal. Embolization of the afferents that are difficult to be accessed in the subsequent open surgery or are the main arteries feeding an AVM seems to be more effective.

3. AVM embolization and resection should be performed within one day, thus minimizing the risk of hemorrhage and edema due to restructuring of blood circulation in the AVM.

4. AVM embolization is a technically complex procedure that must be performed by an experienced team of endovascular surgeons using proven techniques and embolic agents.

Radiation-induced AVM obliteration is based on active endothelial cell proliferation in the walls of blood vessels that is associated with increased myofibroblast activity [12]. Radiosurgical treatment is highly effective in the case of small size AVMs, while irradiation of malformations that are more than 15 cm^3 require multistage treatment or hypofractionated regimen, when the TBD is delivered in a minimum number of fractions at highest doses per fraction. S. Sirin et al. [13] demonstrated that multistage RS result in the best outcomes, allowing the healthy brain tissue to recover between stages of treatment.

The obliteration process is lengthy. Although the first signs of AVM obliteration are detected in patients after 2—3 months according to G. Szeifert et al. [12], complete AVM obliteration is detected in only 50% of patients by the end of the first year of follow-up. After RS, it is achieved in 80% of patients within 2 years and in 90% within 3 years. In our series of cases, the rate of complete AVM obliteration during 3-year follow-up has reached 80.6%, which is a relatively high level.

The risk of radiation-induced complications (in particular, repetitive hemorrhage from an AVM during a latent period after RS) is comparable to the natural course of the disease. As H. Kano et al. showed in a recent study [14], the average risk of hemorrhage in patients 3 years after RS was 5.5%. According to the meta-analysis of H. Kim et al. [15], the rate of repetitive hemorrhage was 4.8% in patients with an AVM who were under follow-up. In our study, a single case of repetitive hemorrhage after irradiation using the Novalis device was detected (5.5%). As previously showed S. Maryashev et al. [16], risk factors for repetitive hemorrhage after RS include hemorrhage in past medical history and a single draining vein.

Presurgical embolization of an AVM significantly prolongs the latency period and adversely affects the

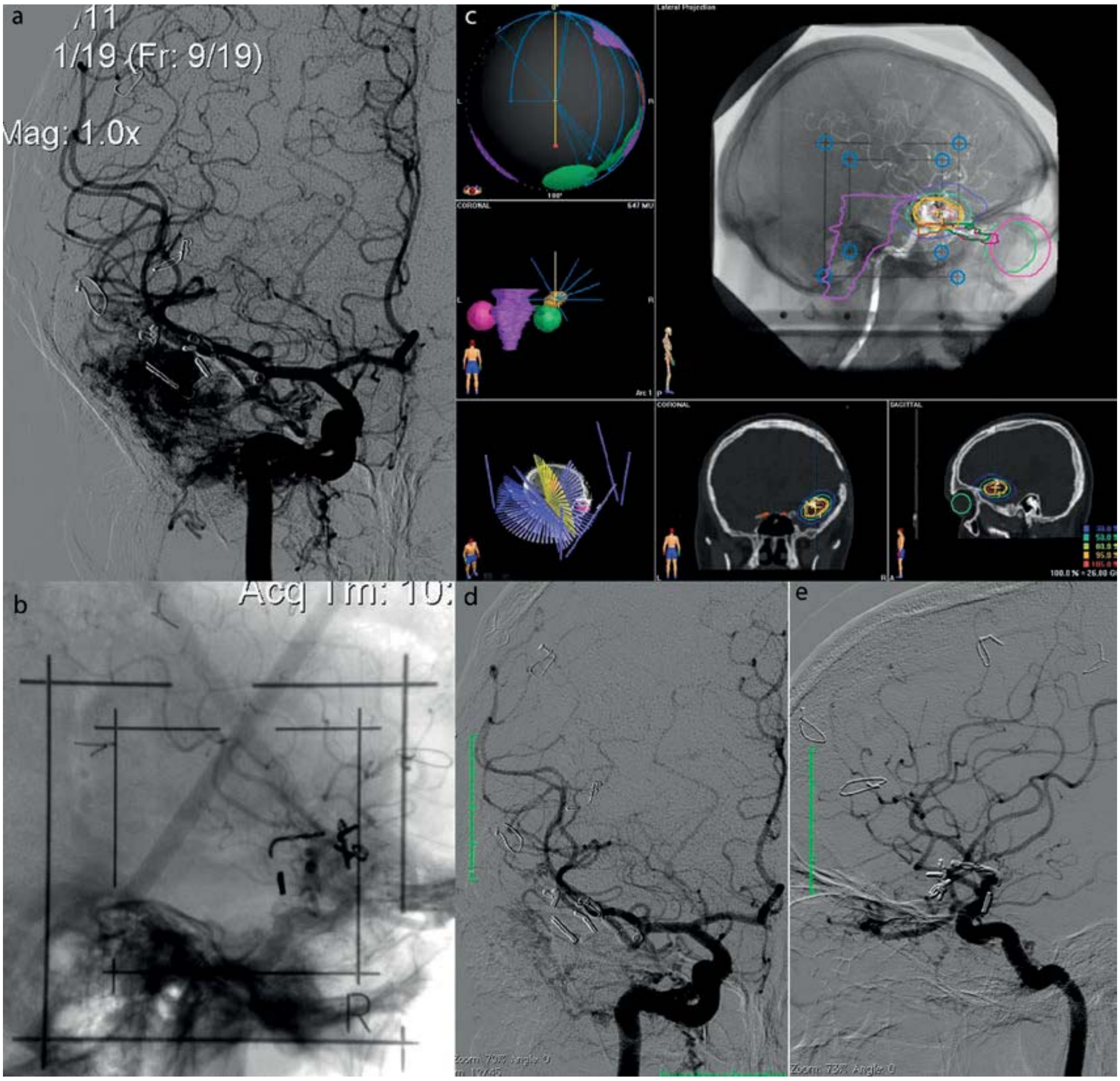

Fig. 5. **Patient A., 31 years of age. AVM in the right temporal lobe.**

a — right-sided carotid angiography reveals an AVM of the right temporal region that is feeding from branches of the right medial cerebral artery and meningeal branches of the external carotid artery; b, c — plan of RS using the Novalis system; d, e — control carotid angiography shows no filling of the AVM.

completeness of obliteration of a malformation [17, 18]. In our view, endovascular treatment of AVMs before irradiation is indicated for hemodynamic aneurysm embolization or partial resection of a functioning part of large multiple AVMs when the size of the nidus requires multistaged fractionated irradiation.

Other causes of incomplete AVM obliteration after RS may be as follows: incorrect assessment of limits/size of an AVM, the lack of necessary 3D-image of a nidus, insufficient dose to achieve obliteration, compression of an AVM with hematoma during irradiation in the subacute stage of hemorrhage, etc. [19].

The group of patients who are considered difficult to treat is presented by cases of large symptomatic AVMs with multichannel blood supply that were located in the critical regions of the brain. The risk of repetitive hemorrhage or progressive symptoms (e.g., epilepsy syndrome) justifies the active treatment strategy but the location and size of a malformation allow for only palliative care. In such cases, endovascular treatment, as indicated above, should be aimed at embolization of hemodynamic aneurysms and large afferents to reduce the blood shunting rate. Partial embolization may have a positive therapeutic effect in patients with refractory epilepsy syndrome or progressive neurological deficit due to reducing venous hypertension or due to steal syndrome. However, palliative embolization of inoperable malformations should be indicated strictly on the individual basis, since it does not reduce the risk of repetitive hemorrhage and does not improve treatment outcomes, as showed O. Kwon et al. [20] and X. Lv et al. [21]. Palliative embolization, in our view, can be considered as a stage of treatment that is prior to SRT and it should be indicated strictly on the individual basis.

Table 10. **Outcomes of AVM embolization in the largest series of patients**

Author, year of publication	Number of patients in the series	Persistent deficit, %	Mortality, %	Glue	Complete occlusion, %
H. Meisel et al., 2002 [6]	450	2.0	1.1	NBCA	16
C.Taylor et al., 2004 [7]	201	9	2	NBCA	–
D. Sahlein et al., 2012 [8]	130	6.2	0.8	NBCA	32.8
V. Katsaridis et al., 2008 [9]	101	8	3	Onyx	27.7
I. Saatci et al., 2011 [5]	350	7.1	1.4	Onyx	51
Yakovlev et al., 2012 [10]	723	4.3	1.3	NBCA/Onyx	30.5

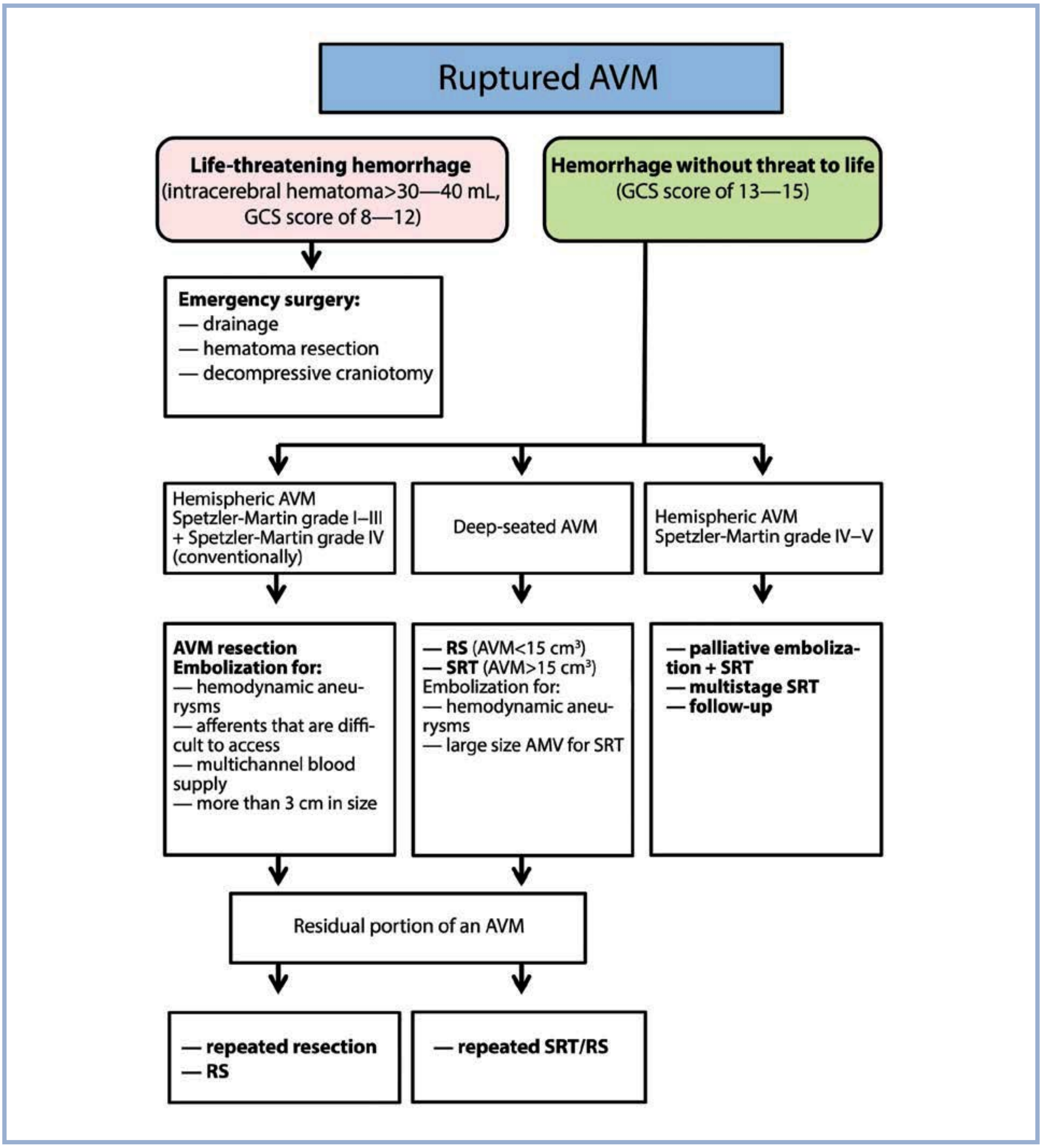

Fig. 6. **Algorithm of the choice of therapy for ruptured cerebral AVMs.**

The risk of RS-induced complications depends upon marginal dose and irradiated volume and does not depend upon the location of an AVM. J. Flickinger et al. specified that radiation-induced changes on the MRI of the brain are identified in approximately 30% of cases in the first 24 months after irradiation. Two third of these patients had edema visualized around the AVM nidus, but this reaction was accompanied by clinical symptoms in only 10% of cases. Corticosteroids for several weeks and the 3-month Trental and vitamin E administration are indicated as a medical assistance for patients with symptomatic radiation-induced edema [22—24].

According to R. Starke et al. [25—28], late (delayed) RS-induced complications include: cysts (1.5%), delayed hemorrhage (0.07%), radiation-induced chronic edema (0.08%), radiation necrosis (0.09%), and radiation-induced tumors (0.02%). The incidence of these complications is low; however, they require surgical treatment in some cases, which confirms the need for a delayed follow-up in patients who underwent RS.

Guidelines

Microsurgical treatment is scheduled for all patients with symptomatic AVMs (grade I—III according to the Spetzler-Martin AVM grading system). In the acute period, surgeries are performed for health reasons and include palliative care (intracerebral hematoma resection, decompressive craniotomy, etc.); AVM resection should be avoided if possible.

Combined surgery should be considered in patients with Spetzler-Martin grade III—IV AVMs. In these cases, indications are determined individually on the basis of the age, clinical presentation, localization, and prospects of AVM embolization.

Preoperative embolization as the first stage of the combined treatment is indicated for deep-seated AVMs with afferents that are difficult to be accessed, as well as for cutting off the blood supply from large vessels to reduce the blood flow before resection. AVM embolization and resection should be performed within one surgical day to minimize the risk of hemorrhage and recanalization of an AVM.

Endovascular occlusion of hemodynamic aneurysms is indicated for all patients prior to AVM resection or radiation therapy.

Endovascular embolization as an isolated therapy should be considered only in patients with minor Spetzler-Martin grade III malformations with a high probability of total AVM occlusion.

Radiosurgery is indicated for patients with an AVM of less than 15 cm^3 when surgical treatment is not indicated due to localization of an AVM, severe condition of the patient, etc. Patients with AVMs more than 15 cm^3 in size are recommended to undergo RS in the hypofractionated regimen. Preoperative embolization before irradiation should be referred as inappropriate, and one should perform it only for palliative care of large AVMs.

Patients with large (more than 6 cm^3), deep-seated, and anatomically complex AVMs with high surgical risk require RS. This therapy should be also considered for somatically preoccupied and severely disabled patients (e.g., after repetitive hemorrhages). Preoperative embolization in such cases is justified for hemodynamic aneurysm occlusion, reducing the rate of blood shunting, and for partial occlusion of an AVM (e.g., bleeding site of a malformation). The algorithm of the choice of therapeutic approach for patients with symptomatic AVMs that is used at the Burdenko Neurosurgical Institute is presented in **Fig. 6**.

Conclusion

The treatment of AVMs remains a challenge to vascular neurosurgery that requires a teamwork of specialists, including vascular and endovascular neurosurgeons, radiologists, neurologists, and anesthesiologists. The decision on the treatment tactics for patients with cerebral AVMs should be determined on the individual basis in each case with regard to clinical experience and available technical capabilities.

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Commentary

Objective. Surgical treatment of arteriovenous malformations (AVMs) remains one of the most significant and difficult challenges for vascular neurosurgeons. As the authors noted, there is a sufficiently large number of hospitalized patients with AVMs (about 120 patients a year) among those who are admitted to the Burdenko Neurosurgical Institute.

Both microneurosurgery and endovascular neurosurgery departments of the Burdenko Neurosurgical Institute are successfully managing patients with vascular diseases. It should be noted that treatment of cerebral AVMs for the past two decades has greatly progressed, mainly towards the development of endovascular techniques. The emergence of new microcatheters, glues (Onyx and NBCA), and seriography with the capability of 3D imaging significantly strengthened capacities of surgery, enabling complex treatment for patients with previously inoperable malformations. At the same time, with accumulation of data on endovascular interventions, as the authors indicated, it became apparent that utter rejection of open surgery is not inevitable. According to various literature sources, complete AVM embolization is just over 50% (depending on the study, glue used, etc.). Meanwhile, the effectiveness of partial embolization remains in question, as the number of authors (e.g., Miyamoto et al.) found that it causes an increased risk of hemorrhage.

In addition, the Department of Radiology of the Burdenko Neurosurgical Institute uses modern SRT systems (the Gamma Knife, Novalis, and CyberKnife devices) since 2009. Thus, the challenge posed by the authors to summarze the data on combined treatment for AVMs is of undoubted interest for specialists.

Study. The authors presented the modern outcomes of combined treatment of 93 patients with AVMs. The study was divided into two fields regarding patients who underwent microsurgical treatment after preoperative embolization of an AVM (40 patients) and patients (53 cases) who underwent SRT after embolization or incomplete resection of an AVM.

Both study groups were classified according to the standard Spetzler-Martin AVM grading system, as well as according to AVM localization, patients' age, selected treatment strategy, and clinical manifestations of the disease.

The outcomes of the combined surgical treatment of patients at discharge and delayed outcomes were assessed on the Glasgow Outcome Scale and were compared to the control group. In most patients (72.5%), more than 50% of an AVM was occluded after preoperative embolization; embolization caused the migration of a glue into the sinus in 1 patient. Good treatment outcomes (GOS score of 4 or 5) were achieved in 35 (87.5%) operated on patients at discharge and in 90% of cases in the follow-up period. Treatment outcomes in the study group were comparable with those of the control group; the latter, however, included less complex cases in terms of surgery: in the study group, 21 (52%) patients had Spetzler-Martin grade III—IV AVMs, whereas there were only 4 (10 %) patients with this grade of AVM in the control group. In selected cases, as the authors showed, embolization enabled to "transform" a more complex AVM into a milder form, without prejudice to treatment outcomes.

Interestingly, in the case of the time of inpatient care and the time of patients in the intensive care unit exceeded the terms expected in the control group, the authors failed to show the impact of embolization on the volume of blood loss during surgeries. The duration of resection of embolized AVMs was found to not differ from non-embolized AVMs in the control group.

The authors demonstrated clinical cases of AVMs in the left cerebellar hemisphere embolized with Onyx and AVMs in the parietal region that were embolized in a few stages using Histoacril. The cases are well illustrated and include data on microscopy of the biopsy material, but do not include intraoperative images, which obviously would have improved the study.

The group of combined radiation therapy included 53 patients who underwent either RS or radiotherapy with three different systems (the Gamma Knife, Novalis, and CyberKnife devices). The group included complex high-risk patients: 25 (47.2%) patients had Spetzler-Martin grade III AVMs and 19 (35%) patients had grade IV—V AVMs. The limit of follow-up was 3 years; the outcomes of radiation therapy in all patients were verified based on the data on selective angiography or MSCT angiography.

In each mode of irradiation, unfortunately, the number of patients was insufficient for statistical analysis and invalid to draw correct conclusions **(see Table 5**). It is worth noting that complete obliteration was obtained in 29 (80.6%) out of 36 patients who underwent RS. SRT performed in patients with large AVMs in the hypofractionated regimen (from 2 to 5 fractions) was less effective as expected: AVM obliteration was confirmed in half irradiated patients. In **Table 8**, the authors presented the outcomes and complications of radiation therapy: single cases revealed worsening of performance status. One patient died from repetitive hemorrhage after irradiation. Thus, the mortality rate was 1.8%.

In the "Discussion" section, the authors argue for a more cautious attitude toward AVM embolization as an independent method of treatment, which nevertheless has significant clinical relevance in certain cases. This section also presents the principles of preoperative AVM embolization with noted need for embolization of high-flux afferents, hemodynamic aneurysms, and difficult-to-access vessels, which helps the surgeon during the subsequent AVM resection.

The authors emphasize the need for limited selective AVM embolization for patients who were scheduled for RS, since the effectiveness of the latter is higher in the case of non-embolized AVMs. At the same time, AVM embolization plays a role in the palliative care of large and multiple malformations. A detailed analysis of the literature data and the validity of the algorithm of choice tactics for treatment of ruptured AVMs accepted in the Burdenko Neurosurgical Institute is an undoubted advantage of the study. Unfortunately, the algorithm does not include asymptomatic and unruptured AVMs.

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