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Multimodality Management in bAVM Surgery - Recent Experience from International Cerebrovascular Fellowship

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ABSTRACT

Background: Arteriovenous malformation (bAVM) presents maldevelopment of the brain's vessels with direct connection between cerebral arteries and veins. By current data, patients from Spetzler Ponce A (SP) are found to benefit from the treatment. Considering outcome, most of SP C and some of the SP B are the most debatable. **Objective:** Arteriovenous malformation presents maldevelopment of the brain's vessels with consequent direct connection between cerebral arteries and veins. Annual risk of haemorrhage in adults is reported for 2-3 %. They usually presents with unilateral headaches seizures and intracranial hemorrhage. By current data, patients from Spetzler Ponce A (SP) are found to benefit from the treatment. Considering outcome, most of SP C and some of the SP B are the most debatable. **Methods:** The study included a cohort of bAVM patients referred to Fujita Health University Bantane Hotokukai Hospital, Nagoya, Aichi, Japan where the main author (AA) has completed international cerebrovascular fellowship under mentorship of Professor Yoko Kato. Japanese Stroke Guidelines (JSG) were used for the treatment decision. Patients were graded according to the Spetzler Ponce (SP) system. Considering American Heart Association criteria (AHA), embolization was used as a part of multimodal treatment. Intraoperative microscopic video tools included Indocyanin green ICG, FLOW 800 and dual image video angiography DIVA. Clinical outcomes were measured using Modified Ranking Score (mRs). **Results:** A total of eleven patients with brain bAVM were studied with the median age of 32 years [IQR = 22-52]. There were ten patients presented with supratentorial and a single patient with infratentorial AVM. Patients were graded according to the Spetzler Ponce (SP) system. There were eight patients in SP A (72,7%), one in group B (9 %) while the rest of them were in C (18 %). Two patients had associated aneurysms which required treatment. The median size of the AVM nidus was 3,50 cm [IQR= 2-5]. Deep venous drainage was found in six patients while three were located in eloquent zones. Clinical outcomes were considered good by mRs <2 in eight patients, seven from the surgically treated group (72,7 % respectively). Surgery median length time was 427, 5 minutes; [IQR =320 - 463] with complete AVM resection in all patients and no mortality recorded in this cohort with the median follow up of 39,5 months [IQR = 19-59]. **Conclusion:** Ideal management of bAVM is still controversial. Those complex vascular lesions requires multimodal treatment in a majority of cases in highly specialized centers. In SP A patients, surgery provides the best results with a positive outcome and small amount of complications. With improvement of endovascular feeder occlusion SP B patients become prone for more positive outcome. Nowadays, intraoperative microscopic tools such as FLOW 800, ICG and DIVA are irreplaceable while improving safety to deal with bAVM. For SP C patients, a combination of endovascular and stereotactic radiosurgery was found to be a good option in the present time.

Keywords: bAVM, FLOW 800, ICG, DIVA, Spetzler Martin (SM), Spetzler Ponce (SP).

1. BACKGROUND

Arteriovenous malformation of the brain (bAVM) presents maldevelopment of the vessels with consequent direct connection between cerebral arteries and veins (1). The prevalence rate 0.01–0.5% equally affecting men and women mostly in early adulthood (2). Annual risk of haemorrhage in adults is reported for 2-3 % (3) while pediatric population carries 61-68 % risk with possible worse neurological outcome. If they had ruptured, the risk of haemorrhage is increased in the first year with a range of 4.8 – 15.7 % (4) while for the unruptured ones the risk was found as 1.3 % (5). Features

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such as associated aneurysms, single drainage vein, restriction of the venous outflow, posterior fossa and eloquent locations were found to carry a higher rupture risk. (6). They are usually sporadic. However, they may be found multifocal in autosomal-dominant disorders, mostly in hereditary hemorrhagic telangiectasia and capillary malformation (CM). Except Osler-Weber-Rendu syndrome they may be presented in association with cutaneous forms of CM while some studies reports mutations in non *Rasa1* patients. Arteriovenous malformation usually presents with unilateral headaches due to raised intracranial pressure or steal phenomenon, seizures and intracranial hemorrhage (7). Considering the outcome of hemorrhage, some reports found more favorable in AVM compared to other causes. By current data, patients from SM grade 1 and 2 (SP A) are found to benefit from treatment. Considering outcome, most of SM grades 4&5 (SP C) with some of the SM grade 3 (SP B) are the most debatable (8).

2. OBJECTIVE

The aim of this study was to present current multimodal bAVM management in high volume WFNS declared center. International fellowship in cerebrovascular surgery provides an unique opportunity for a young neurosurgeon to become familiar with this rare and complex brain vascluar lesions and their optimal treatment.

3. PATIENTS AND METHODS

A retrospective study of a cohort of 11 bAVM patients who were referred to Fujita Health University Bantane Hotokukai Hospital, Nagoya, Aichi, Japan between 2014-2019 was performed during main authors (AA) international cerebrovascular fellowship under the mentorship of Professor Yoko Kato. Due to the small cohort with those complex lesions, median and interquartile range (IQR) were used. Patient preoperative presentations, grade assessment and treatment modalities were analyzed with focus in microsurgery combined with video adjuncts. Japanese Stroke Guidelines (JSG) from

were used for the treatment decision in our cohort (9). Spetzler Ponce (SP) A (Spetzler Martin - SM I and II) and SP B (SM III) grade patients were treated surgically (10). Considering American Heart Association criteria (AHA), embolization was used as a part of multimodal treatment for the management of bAVM with deep arterial feeders in understaging purposes for SP B patient. Clinical outcomes were measured using Modified Ranking Score (mRs). Postoperative radiological evaluation included Computed Tomography Angiography (CTA), Magnetic Resonance Imaging and Angiography (MRA) in all patients.

4. RESULTS

Demographic data and patient presentation

A total of 11 patients with brain bAVM were referred in this study. The median age was 32 years [IQR = 22-52]. Six male and five female patients were found. There were ten patients presented with supratentorial and a single patient with infratentorial bAVM who was presented with bleeding initially. From those patients with supratentorial location three patients presented with bleeding. Five patients were found incidentally while two had seizures as an initial symptom. For easier interpretation we divided patients in three groups according to the Spetzler Ponce (SP) grading system. However, five groups Spetzler Martin grading system is also used and considered in assessment for treatment decision making. Eight patients were found in SP group A (72,7%), one in group B (9 %) while the rest were in C (18 %). From those SP C, there were two patients in grade IV by SM grade while one presented with grade 5. Two patients had associated aneurysms which required treatment, one by coiling in SP A. In second patient from SP C group, associated aneurysm caused intracerebral hematoma requiring surgical treatment and clipping.

Treatment modalities and outcome

All patients were subjected to two-dimensional (2D) and three-dimensional (3D) computed tomography angiography (CTA), with 3D digital subtraction angiography (DSA) and magnetic resonance imaging

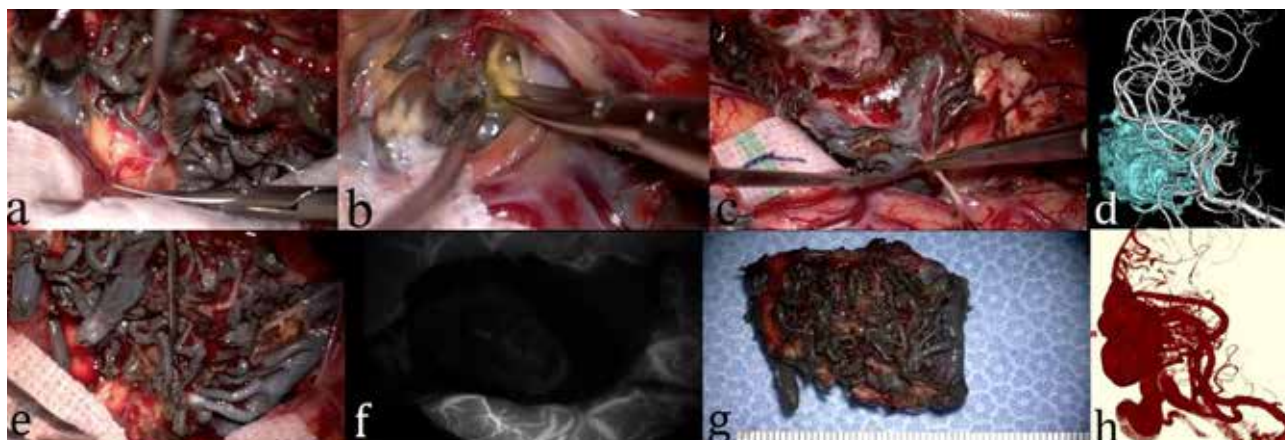


Figure 1. Image a; Deep dissection, and arterial feeder identification. Image b; The hemosiderin changes in the deep white matter. Image c & d; Superficial vein is cauterized and the nidus is completely divided from all vessels. Image e: Deep dissection of previously embolized bAVM. Image f & g: ICG shows the completely divided nidus from the rest of the cortex (diameter after resection 3,8 cm). h: Comparative image with bAVM 3D DSA in ap view. Provided with courtesy of Professor Y. Kato., Fujita Health University, Bantane Hotokukai Hospital, Nagoya Japan; 2018.

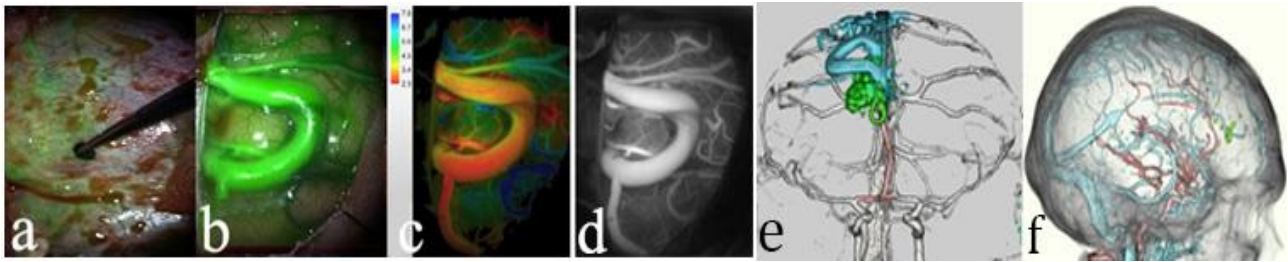


Figure 2. Image a: DIVA before dural opening. Please note dural transparency in green collar. Image b: DIVA shows large vein loop. Two vessels are connecting to the vein without vein-artery differentiation. Image c & d: Flow 800 and ICG comparative image. The color map shows arterialized vein (red color, 2,3 seconds inflow). Some normal veins are noted on the cortical surface (blue color). Image e: 3D CTA of bAVM nidus (green color) with large draining vein (blue color). Image f: Postoperative 3D CTA shows complete bAVM resection. Provided with courtesy of Professor Y. Kato., Fujita Health University, Bantanne Hotokukai Hospital, Nagoya Japan; 2020.

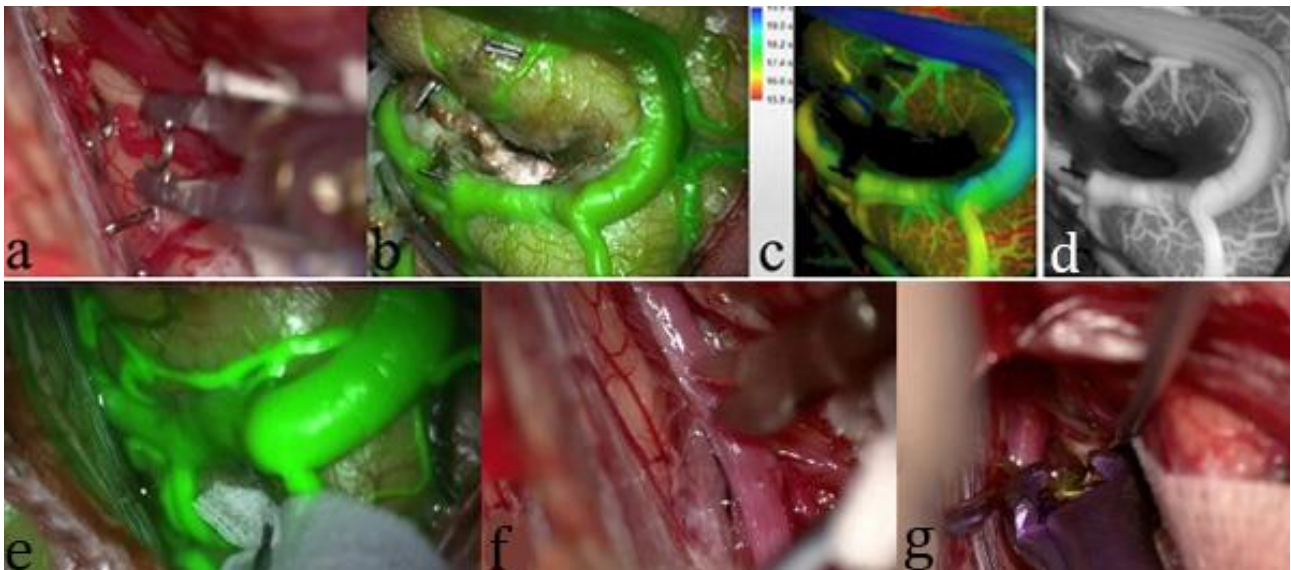


Figure 3. Image a: Mini clips are used for feeder occlusion. Image b: DIVA after clipping. Note reduction in the vein diameter after clipping of one of the feeders. Image c: Flow 800 shows delayed filling. There is a less arterialized blood filling the vein. Distal part of vein shows normal color pattern. Image d: ICG filling on the right side of the image without possibility of distinction in filling phases. Image e: Contrast enhancement and deep course of the vein. Image f: Pericallosal artery dissection from which the deep perforators have been noted. Image g: Clip is applied to the deep perforator without changes in MEP. Provided with courtesy of Professor Y. Kato., Fujita Health University, Bantanne Hotokukai Hospital, Nagoya Japan; 2020.

(MRI). By using the Japanese guidelines criteria (JGC), all patients from SP A (SM 1 and 2) and SP B (SM 3) were treated surgically, while there was a single patient from group C (SM 5) with previous multiple bleedings. All surgically treated patients were treated by Professor Yoko Kato and her team and analyzed by main author during the cerebrovascular fellowship period. Considering AHA criteria eight patients were treated by preoperative embolization, six in SP A group and all patients from SP B and SP C groups. Two patients were treated as emergency cases after hemorrhage while the rest of them underwent elective treatment. From those urgently treated, one patient was presented with hemorrhage after embolization. One patient from SP C group underwent embolization and gamma knife treatment without surgery. The median size of the AVM nidus was 3,50 cm [IQR= 2-5]. Deep venous drainage was found in six patients while three were located in eloquent zones. Vascular board meetings have been conducted for all elective cases prior to surgery. A graphical simulation was

used to decide on the best surgical approach. All surgeries were performed under general anesthesia. Advanced microsurgical technique were used. Vessel dissection and nidal coagulation with nonsticky bipolar were found to be useful in bAVM surgery and Sugita Mizuho microclips were used for feeder occlusions. All operations were performed using operating microscope (Carl Zeiss Co., Germany). Intra operative video assisting tools such as Indocyanin green (ICG) were used in all except one patient while dual image video angiography (DIVA) was used since 2016. Depending on availability a near infrared video camera with FLOW 800 software was used in three cases. In a single patient with a diffuse subarachnoid hemorrhage (SAH) associated aneurysm was found to be the source of bleeding. After initial aneurysm coiling and bAVM feeder occlusion, the patient underwent surgical treatment with a good outcome (mRs0). Clinical outcomes were considered good by mRs <2 in eight patients, seven from the surgically treated group (72,7 % respectively). One patient had a mRs 3 while two were

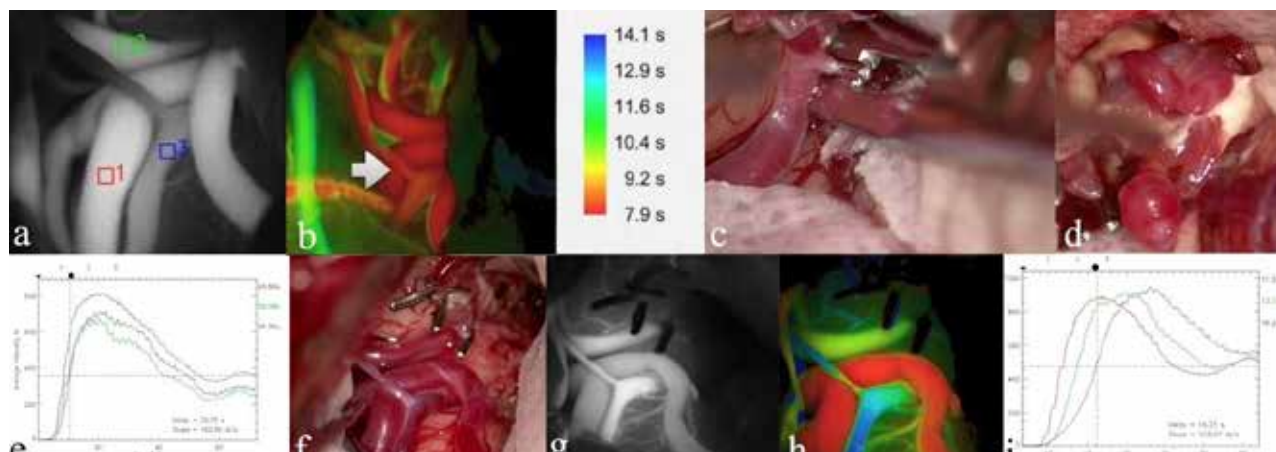


Figure 4. Image a: ICG after Sylvian fissure dissection. The vessels are numbered: 1 M2 branch; 2: feeder, 3: draining vein. AVM nidus is fed by M2 branch. Image b: FLOW 800 after injection. Please note the arterialized vein marked with an arrow. Image c: MEP changes after feeder clipping. The clip was moved immediately. Image d: Permanent feeder obliteration with mini clip. Image e: MEP changes in the patient with a decreased potential. Image f: After resection of the nidus, preserved vessels are seen. Image g: ICG after resection shows the filling of the Sylvian fissure arteries and vein. Image h: FLOW 800 after resection shows preservation of all vessels with normal venous filling according to the start of the surgery (Image b). Image i: MEP signal is now normal with full potential. Provided with courtesy of Professor Y. Kato., Fujita Health University, Bantanne Hotokukai Hospital, Nagoya Japan; 2019.

found with a severe grade of mRs (4 and 5 respectively). Another patient with large intracerebral hematoma and SAH from SPC C group (SM V) had associated an aneurysm on ICA treated by clipping in earlier surgery. The same patient presented with multiple episodes of bleeding from large bAVM in eloquent cortex during observational time. Patient underwent surgical resection of bAVM after four times preembolization with poor clinical outcome (mRs 5). Another patient (SP A; MS 2) was urgently treated due to a hemorrhage after embolization with good outcome (mRs 0) after surgery. Same patient referred earlier as repeated SAH. From other postoperative complications one patient had a small residual hematoma in surgical field in control CT exam. Patient was only observed and discharged from hospital (mRs 0) with normal brain MRI/MRA after four months. Surgery median length time was 428 minutes; [IQR = 320 - 463]. In all patients complete bAVM resection was achieved. There was no mortality recorded in this cohort with the median follow up of 40 months [IQR = 19-59] for surgically treated patients.

Illustrative case 1

A 20-year-old male presented with seizures. MRI showed right temporoparietal bAVM with 3,8 cm nidus diameter. 3D CTA and DSA were performed to assess the anatomy and malformation complexity. Deep arterial feeders from the medial cerebral artery (MCA) and internal carotid artery (ICA) were identified. Venous drainage included four superficial veins with inflow to the Sylvian veins and superior sagittal sinus (MS 2, SP A). Presurgical embolization was performed in two occasions and patient underwent surgical treatment by right frontotemporal craniotomy. Intraoperative ICG was used to identify the relation between the nidus, feeders and veins. Some hemosiderin imbibition of the deep white matter was identified from previous bleeding which earlier has not been reported. Complete nidus and drainage vein resection was performed. Operative

procedure length was 437 minutes. The postoperative course was uneventful with a good clinical outcome during 61 months follow up period. MRI and MRA after a year showed complete resection with a normal blood flow pattern (Figure 1).

Illustrative case 2

A 32-years male presented with bAVM in the left parietomesial region in the MRI. 3D CTA showed a 54,3 X 44,7 mm large nidus with deep arterial feeders from the MCA, posterior cerebral artery (PCA) and distal anterior cerebral artery (DACA) branches. Deep venous drainage was identified with pineal region and sinus rectus inflow (SM 3; SP B). The patient underwent four times presurgical embolization and bAVM resection was performed through the right parietooccipital craniotomy. MEP has not shown changes during surgery. ICG and DIVA were used prior to the dural opening, during dissection and after nidus resection. FLOW 800 was used to identify relations between normal cortical veins of the motor zone and temporomesial located draining vein. Full nidal resection with the drainage vein was achieved. The postoperative course was uneventful, the patient was discharged from the hospital fully independent. CT and 3D CTA showed complete resection with postembolization material. Control MRI after a year showed complete bAVM resection (Figure 2).

Illustrative case 3

A 32-year-old male presented with headaches. During screening and evaluation 3D CTA was performed. A 2 cm large nidus of the bAVM in the right frontal region with deep venous drainage (SM 2, SP A) was found in right frontal lobe. A single embolization followed by surgery was performed in 2018 through right frontal craniotomy. ICG, DIVA, FLOW 800 and MEP were used during surgical resection. Complete nidus and draining vein were totally resected with operative time of 209 minutes. Microscope video tools confirmed total extirpation of the bAVM with vein drainage exclusion and

preservation of the normal cortical vein. The postoperative course was uneventful. Postoperative 3D CTA confirmed total resection without residual bAVM (Figure 3 and 4).

Illustrative case 4

A 29-year-old female presented with 3D CTA which showed bAVM in the left frontal lobe with 2 cm large nidus and deep venous drainage. Surgical treatment was performed in 2016 (surgical time 462 minutes). Intraoperatively ICG, MEP and FLOW 800 were used. During temporary clipping of the large feeder MEP showed changes and the clip was replaced without further changes. Differences in FLOW 800 were noted prior to and after nidus resection. The patient was discharged from the hospital neurologically intact in follow-up period of 26 months. A year after surgery MRA showed a normal vascular pattern.

5. DISCUSSION

Management of unruptured brain arteriovenous malformations (ubAVMs) is still controversial. Of the most controversial studies favoring conservative instead of the interventional treatment was ARUBA (11). However it seems impossible to calculate every single combination for different AVM variations. Balancing the risks and hazards for each grade, final decision should be made according to the different occasions. Careful multidisciplinary team assessment should be performed for each case. Interventional treatments includes embolization, microsurgical resection, or stereotactic radiosurgery with the final goal of total nidus obliteration. Since 1986, surgical risks are widely influenced by the MS grading system. Additional introduction of SP simplified scoring system to three classes (12) while Lawton-Young supplemented scale also played an important role in treatment decision. Lawton et al. observation of SM grade 3 patients showed much worse functional outcomes and a higher mortality in AVMs with nidus 3 - 6 compared to those with 3 cm size but with deep venous drainage even if both of them are located in an eloquent zone. Size followed by eloquence is found as most important predicting factor for functional outcome. According to the size in SP C grade (SM 4 and 5) the European Consensus agreed that surgery is not the first option. Size was found to be more important factor according to the eloquence (13). We found nidus resection convenient in most of cases with median size of 3-4 cm. Primary surgical approach followed by some of the treatment modalities were found to be the basic treatment option. Considering JSG, SP group A and B bAVMs are found to benefit from surgical treatment in our study. In a recent critical review of bAVM surgery Morgan et al found that SP A patients expecting a good quality of life for the next 8 years are likely to do better with surgery in expert centers instead of remaining untreated (14) comparing to other study which reports lower risk for stroke or death in ARUBA-eligible patients ($P < .0001$) with multimodal treatment based on microsurgery combined with embolization. Scottish Intracranial Vascular Malformation Study reported 40% mortality or dependen-

cy (mRS score >3) if patients experienced hemorrhage from bAVM while other single-center study have found a good functional outcome (mRS <2) in 72 % of those patients (28). If the bAVM caused bleeding, SP C could also be considered but the clinical outcomes are poor.

Surgical treatment is relatively safe with a 1.4% complications in SP A and 20 % in SP B group while complications of SP C were found in 41% (15). Recent meta analysis found 96% rate of AVM resection followed by obliteration in 38 % of patients treated by gamma knife and 13 % in endovascular treatment. Other meta analysis reported surgically treated ubAVM carries a 0.3% mortality rate, 2.2% morbidity rate, and 0.3% postoperative hemorrhage rate (16). Schramm et al reported no mortality in SM 1 and 2 of ARUBA eligible patients while 3,2 % were found with a permanent neurodeficit (17). Still, new study of Mohr et al. reports class II evidence for increased risk of disability and death. Same study proposes interventional management to be deferred in anticipation of a haemorrhage which may never occur (18). Our results showed no relation between stroke and surgical treatment. One patient presented with hemorrhage after embolization possibly due to higher risk and the patient underwent urgent surgical treatment but with persistent neurosequelae (mRS 4). It is known that a worse functional outcome can be found in patients with small size but deep venous drainage (DVD). In MS 2 patients DVD is considered more important for the surgical outcome compared to the eloquence or if the long draining vein is presented. However, we haven't noted any differences in outcomes according to the size - DVD relation in SM II (SP A) group. Two patients presented with DVD with good uneventful surgical course and good postoperative outcome.

Brain malformation surgery can be challenging especially if the feeder arteries and draining veins are not directly visible on the surface. Still, surgical risk is likely to be less than risk of hemorrhage in a 6 years of natural history for SP A patients (19). and it represents first option in order to eliminate the risk.

In our study most of the surgically treated patients were SP grade A (SM 1 and 2) with good clinical and radiological outcome comparable to similar studies. Complete resection was achieved in all treated patients with no residual bAVM in postoperative CTA and MRA. Some postembolization material is seen in multiple CTA scans with normal vascular patterns. No mortality was reported while postoperative edema requiring bone decompression was found in a single patient with SP C (SM 5). There was one patient with small postoperative hemorrhage in surgical field who has not required surgical reexploration (mRS 0).

Considering location, temporal lobe was found protective from unfavorable outcomes and it can be resected if necessary (20). Majority of our patients had an bAVM in the temporal and frontal region except a single one in parietomedial region from SP B group. All bAVMs were safely resected with a positive radiological outcome.

Considering JSG and AHA criteria all the patients underwent surgical resection after preembolization in majority of our patients due to a deep arterial feeders. Nowadays, embolization is used as an adjuvant therapeutic modality for AVMs in a majority of cases (21). We found nidus blood supply excluding to be easier followed by convenient nidus dissection (Case illustration 1). By Lawtons observation, patients from SP B (SM III) could benefit from surgery after understaging by embolization. Even some reports shows no significant influence of endovascular treatment in outcomes for higher grades, we consider it important due to understaging. In our series one patient from SP B group presented with large nidus, close but without direct involvement of eloquent motor zone. Multiple large deep arterial feeders were identified.

Considering risk and patients age we performed surgical treatment after four times preembolization. Complete bAVM resection was achieved with good outcome in 15 months follow up period (mRs 0) (Case illustration 2). Those patients should be carefully selected. However, if there are limited number of feeders in surgically inaccessible areas, a standalone embolization could be an option.

Due to very high complication incidence in SP C patients, surgical treatment is limited. We treated one patient after multiple episodes of hemorrhages and endovascular treatment in four occasions. A 6,5 cm large nidus in an eloquent zone, multiple deep feeders from MCA and multiple deep veins were the main problem to deal with. Postoperatively, the patient presented with right hemisphere edema requiring urgent bone decompression possibly due to a vascular accident. The outcome of the treatment was found poor with persistent neurological deficit (mRs5). Compared to other reports even SM grades 3 and 4 were found to be associated with increased risk. The chance for new deficit for SP grade B and SP C was found as high as 32 and 73 % respectively. Despite advances in other modalities surgical extirpation is still represents the main treatment option (22).

Nowadays, small but also moderate bAVMs are treated by gamma knife [42] with persistent risk of hemorrhage in 3-4 years after SRS treatment. After latency period, obliteration based on location ranges between 47% and 90% (23). While radiosurgery decreased the radiation induced complications there is still lack of obliteration especially in the early phase. In our cohort a single patient from SP C (SM 4) group was treated by combination of endovascular and SRS modalities with good clinical outcome in a first year of follow up period (mRs1). It is important to know that high SM grades and irregular shape are more prone for gamma knife failure (24) while pre SRS embolization is found in negative correlation with obliteration (25).

In recent times many additional tools were developed in order to increase the safety and improve surgical resections. To recognize residual nidus during surgery, Takagi et al. described Indocyanin green-videoangiography (ICG VA) (26). Veins, which may be found adherent to the dura can be easily recognized early prior to

dural opening. In 2011 Kato et al. reported a valuable microsurgery addition to the conventional ICG and Doppler ultrasound. Flow 800 represents an analytical color map visualized by a microscope (22). Identification of blood direction via the fluorescence presents the bAVM hemodynamic and it is safe for the patients and staff and it can be repeated multiple times. Shah and Cohen – Gadol found ICG with FLOW 800 efficient and noninvasive which helps to identify arterialized veins and their flow status during bAVM surgery (27).

Limitations as deep seated vessels flow are overcome by meticulous dissection and deep structure exposition. Some new studies reports sodium fluorescence in video angiography as a simple and low-cost technique but in a short series of patients. ICG is used in all treated patients. It helps surgeon to understand basic intraoperative vascular relations during operative stages. FLOW 800 is extremely important for differentiating arterial feeders and drainage veins from normal vessels (Case illustration 2, 3, 4).

Furthermore DIVA is introduced to Department at Bantan Hospital, Fujita since 2016. Intraoperative normal brain visualisation, precise normal vessels, feeders and draining veins distinction is a main advantage (Case 2, 3, 4). Also, the surrounding brain is visible compared to ordinary ICG. Additionally, it helps to identify any residual part of the nidus after resection while providing information about normal vessels passability.

6. CONCLUSION

Ideal management of bAVM is still controversial. Those complex vascular lesions requires multimodal treatment in a majority of cases in specialized centers. In order to get fully acquainted with the best possible treatment, newer technologies and options of multimodal bAVM, cerebrovascular fellowship in a world-renowned high-volume center is of great importance for young neurosurgeons. Nowadays, intraoperative microscopic tools such as FLOW 800, ICG, MEP and DIVA are irreplaceable in modern neurosurgical era while improving safety to deal with complex bAVM vessels.

In an SP A patients surgery provides the best results with a positive outcome and small amount of complications. With improvement of endovascular feeder occlusion SP B patients become prone for more positive outcome while rate of complications is becoming lower. For SP C grade patients, a combination of endovascular and stereotactic radiosurgery was found to be a good option in the present time.

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- **Conflict of interest:** The authors declare no conflict of interests.
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