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REVIEW

Endovascular and Percutaneous Embolotherapy for the Body and Extremity Arteriovenous Malformations

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Abstract:
Arteriovenous malformations (AVMs) consist of abnormal communications between the arteries and veins. They can involve any part of the body and extremity and grow in proportion to age and in response to hormonal influence or trauma. When symptoms progress from Schöbinger clinical stage II to III, transcatheter and/or direct puncture embolization are less-invasive and repeatable options for symptom palliation. The goal of embolization is to obliterate the AV shunt, and the choice of lesion access and embolic agents is based on the individual anatomy and flow. Embolization can be technically challenging due to complex vascular anatomy and morbidity risks. Therefore, a multidisciplinary management is essential for the diagnosis and therapeutic intervention of AVMs.

Keywords:
arteriovenous malformations, arteriovenous fistula, arteriovenous shunt, embolization, embolic agents

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Introduction

Arteriovenous malformations (AVMs) are fast-flow vascular malformations consisting of abnormal communications between feeding arteries and enlarged draining veins. AVMs are often described as congenital lesions; however, *de novo* formation or acquired nature of brain AVMs has been recently indicated in the context of genetic abnormality [1]. Peripheral AVMs can occur most commonly in the head and neck (47%) and also involve the extremity (29%) and the trunk (11%) [2]. AVMs generally enlarge in proportion to age, and the increase in lesion size and shunt flow causes various symptoms, such as pain, ulceration, bleeding, dysfunction, and ultimately high-output cardiac failure. Puberty, trauma, pregnancy, and surgical procedures are known risk factors for symptom aggravation. To date, no systemic therapy has yet been established for AVMs; thus, locoregional treatments, mainly surgical and/or endovascular therapies, are the treatment of choice for patients with symptomatic AVMs. Among them, embolization is a minimally invasive and repeatable treatment option for unresectable AVMs. Interventional radiologists should be familiar with the interpretation of AVM angioarchitectures and handling of various embolic agents to avoid ineffective treatment and severe complications. In this article, the indication, technical considerations, and clinical outcomes of embolization for the body and extremity AVMs (BE-AVMs) are reviewed.

Indication and Goal of Embolization

Symptoms of AVMs tend to progress and become severe over years according to Schöbinger's clinical stages [3]. In stage I (quiescence), AVM is asymptomatic with skin redness or warmth and mimics capillary malformation. In stage II (expansion), AVM becomes warmer and larger with pulsation, bruit, thrills, and tortuous veins. In stage III (destruction), the symptoms become more significant with pain, ulceration, bleeding, and infection. Stage IV (decompensation) is defined as AVMs associated with high-output cardiac failure. Liu et al. evaluated the natural progression of extracranial AVMs, including lesions of the head and neck, body, and extremities (n = 272). They reported that children with stage I AVM had a 44% risk of progression to stage II or higher stages before adolescence and as high as an 83% risk

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before adulthood with the mean age at progression of 13 years. Diffuse AVMs were more likely to progress than localized lesions ($P < 0.001$), and recurrence was less likely when lower-staged AVMs were treated ($P < 0.001$). Resection with or without embolization had a lower recurrence rate (81% vs. 98%, $P < 0.001$) and longer time to recurrence than embolization alone (43% vs. 14% >1 year, $P <$ 001) [4]. Therefore, embolization may be considered for unresectable AVMs with worsening of symptoms, functions, and cosmetics, but it is important to weigh the balance between the procedural risks and symptom severity in each patient [5].

Pretreatment Evaluation

In most cases, the diagnosis of AVMs can be made *via* careful medical interview and physical examinations at outpatient clinics. Aside from physical examinations, ultrasound with color-coded Doppler is helpful in confirming and analyzing the fast-flow shunting of AVMs. Ultrasound is also indispensable for intraprocedural monitoring of blood-flow reduction by embolization. Contrast-enhanced CT and MRI are also useful for further evaluation of the lesion extent and the deep tissue involvement, including bones and joints. Recently, dynamic 4D-CT imaging and time-resolved 3D-MR angiography have been employed to analyze the detailed vascular anatomy and flow dynamics of AVMs [6, 7]. Catheter-based angiography is not routinely performed for the purpose of diagnosis; however, digital subtraction angiography (DSA) with high-frame rates and rotational 3D-/4D-DSA offers full depiction of the affected arteries and veins to make a detailed planning of the lesion access and embolic agents before embolization.

Angiographic classification

AVMs are generally considered to have the so-called "nidus" consisting of the complex tangled vessels between the feeding arteries and draining veins without intervening capillaries. However, not all AVMs have such a classical nidus but rather often form various types of fistulous connection with arteriovenous (AV) shunt. The goal of embolization is symptom improvement *via* selective occlusion of the portion of the AV shunt. Occlusion of the AV shunt is often anatomically and technically challenging with the risk of normal tissue ischemia and systemic escape of embolic agents through the shunt. Therefore, it is important to analyze the angioarchitecture of the AVM for the appropriate choice of access routes and embolic agents. Cho et al. proposed an angiographic classification of BE-AVMs [8], which modified the original classification for intracranial AVMs by Houdart et al. [9]. Cho's type-I AVM is a large arteriovenous fistula (AVF) between no more than three feeding arteries and the single dominant outflow vein (DOV). In the type-I AVM, transarterial embolization (TAE) is considered to reach the fistulous portion from the end of the feeding artery to the DOV. Cho's type-II AVM consists of multiple small feeding arteries shunt to DOV, and the AV shunt is present in the DOV wall. TAE is considered to reduce arterial inflow to the shunt; however, it may not always result in complete occlusion of the AV shunt in the vein wall. Therefore, direct puncture embolization (DPE) or retrograde transvenous embolization (TVE) may also be needed to occlude DOV. Cho's type-IIIa and type-IIIb AVMs consist of non-dilated and dilated AVFs between multiple feeding arteries and draining veins, respectively. In the type-IIIa or IIIb AVM, TAE and/or DPE are considered to occlude the fistulous component, whereas it is usually difficult to do with TVE. In addition, Ko et al. proposed a new subclassification of Cho's type-II AVM: type IIa (multiple arterioles shunt to the focal segment of single DOV, i.e., equal to the original type-II), type IIb (multiple arterioles shunt to the venous sac with multiple draining vein), and type IIc (multiple arterioles shunt along the long segment of the draining vein) [10]. They recommend the strategy to occlude the venous segment by DPE or TVE regardless of the subtypes.

Another angiographic classification was proposed by Yakes [11, 12]. Yakes type-I is a direct arteriovenous connection often observed in pulmonary and renal AVFs. Yakes type-II has a classical "nidus," as previously described. Yakes type-IIIa and type-IIIb have multiple feeding arteries shunt to an enlarged single DOV and an enlarged aneurysmal vein with multiple dilated outflow veins, respectively. Yakes type-IV has innumerable micro-arteriovenous connections infiltrating an entire tissue with capillary beds. This type is not described in Cho's classification, but the normal post-capillary veins compete with the arterialized venous outflow from AVF causing venous hypertension in the involved tissues.

Although not all AVMs can be simply classified into these types, it is helpful to understand where to occlude by what approach and what embolic agents based on the anatomy of AVM. Irrespective of the type, the transitional portions between the feeding arteries and draining veins are considered as the real target of embolization.

Embolic Agents

Various embolic agents have been used to treat AVMs, but they should be chosen according to the individual vascular anatomy and flow condition. Liquid agents, mainly n-butyl cyanoacrylate (NBCA) and ethanol, have been mainly used as primary agents to occlude the AV shunt.

NBCA or glue is usually mixed with iodized oil (Lipiodol, Guerbet) at a rate of 10%-50% to obtain radiopacity and increase the polymerization time according to the vessel size, blood flow, and microcatheter position. Acute inflammation is induced around the vessel wall and the surrounding tissue, and there is a concern that palpable foreign body mass remains with the risk of infection in case of AVMs involving the skin or mucosa.

Ethanol has a strong sclerosing effect on the endothelial cells, and endothelial damage induces acute thrombosis and vessel occlusion. Ethanol should be injected only when the operator is confident that the catheter or needle is within the

AV shunt because non-target embolization may lead to tissue necrosis and nerve damage [13]. Embolization using ethanol requires general anesthesia, because ethanol injection is very painful and also has systemic effects. In the previous studies, limiting ethanol dose to 0.14 mL/kg per single bolus injection with a 10-min interval [14] or total ethanol dose to 0.5-1.0 mL/kg per session was proposed to prevent pulmonary vasospasm and hemodynamic collapse [10, 15, 16, 17]. For AVMs involving the skin or capillary beds (Yakes type-IV), dilution of ethanol to 50:50 mixtures with nonionic contrast media may be safer to avoid skin necrosis [12, 13].

Recently, Onyx, a non-adhesive liquid agent composed of ethylene vinyl alcohol copolymer (EVOH) dissolved in DMSO, has been used for peripheral AVMs [18, 19]. Onyx allows controlled injection using the so-called "plug and push technique" to achieve antegrade filling of the AVM with soft "lava-like" cast. As Onyx has less thrombogenicity compared with NBCA or ethanol, a large amount of the liquid is needed to obtain sufficient occlusion of the AVM. It requires very slow or multiple injections under fluoroscopy guidance for several minutes associated with an increase in radiation exposure. Onyx also requires the use of specific DMSO-compatible microcatheters. There is a concern of tattoo effect by the tantalum powder in case of superficial AVM.

As adjunctive agents, coils are often used in outflow veins before injecting liquid agents. Coils decrease the volume and flow of outflow veins so that liquid agents such as ethanol can sufficiently come into contact and destroy the endothelial cells of the lesion [17]. However, coils should not be used to occlude the proximal feeding artery because it will recruit new collaterals to the AV shunt and make the subsequent TAE difficult.

The use of polyvinyl alcohol (PVA) particles or microspheres is limited to the treatment of AVMs as they may pass through the AV shunt. However, they are sometimes helpful in reducing arterial inflow of diffuse micro-shunts and improving symptoms. Particularly, inert and calibrated microspheres can penetrate into the shunt vessels corresponding to the particle size but do not reach capillary beds, thus preventing microcirculation of and ischemic damage to the normal tissues [20].

Embolization procedures

Arterial angiography is always needed to evaluate the baseline anatomy and blood flow of the AVM and also to monitor the degree of devascularization regardless of approaches to the AVM. Due to the fast-flow condition of AVMs, blood flow control using manual compression, tourniquet, or a balloon catheter may help control the delivery of embolic agents. However, flow cessation of both the arteries and veins using tourniquet carries a risk of reflux of embolic agents into the adjacent normal branches. Furthermore, tourniquet release following long venous stasis can cause rapid escape of sludge or thrombi from the outflow veins, which may affect cardiopulmonary function. In contrast, a balloon occlusion of the feeding artery decreases the arterial pressure, but the antegrade flow into the AV shunt would still remain. Even if a normal artery branches off the feeding artery, its flow direction will be reversed into the AV shunt, which prevents migration of embolic agent into the normal tissues [21, 22]. In TAE using ethanol, a delivery microcatheter should be advanced as close as possible to the AV shunt beyond any branch supplying normal tissues. Then, test angiography is performed with or without blood flow control to evaluate whether ethanol can be safely injected into the AV shunt and estimate the volume of ethanol. Ethanol should be intermittently injected at a 5-10-min interval, and angiography is repeated to confirm the gradual decrease in the shunt flow. In TAE using glue, glue is continuously injected under DSA from the distally placed microcatheter to achieve penetration into the AV shunt, although precise prediction of the occlusion level is difficult. Injection of warmed glue with reduced viscosity *via* a triaxial micro-balloon system is helpful in preventing the reflux and improving distal penetration of glue [23]. The "plug and push technique" similar to that for Onyx also enables progressive filling of glue into the AVM after creation of a glue plug around the catheter tip [24]. Once the target vessel is occluded by glue, the delivery microcatheter should be immediately removed to avoid gluing of the microcatheter to the vessel wall. In DPE, the AV shunt is accessed by needle puncture under ultrasound or fluoroscopy guidance. Then, if blood comes out from the needle, angiography is performed by hand contrast injection to assess whether the needle tip is located within the intended portion of the AV shunt. An 18G long needle can be used for the direct delivery of 0.035-inch pushable fibered coils or as an entrance of a microcatheter for the delivery of various microcoils. For injecting liquid agents such as NBCA and ethanol, a 23G or smaller needle connected to an extension tube with a small lumen volume is used to minimize the residue of agent in the dead space.

In Cho's type-I or Yakes type-I AVM with macro-AVF, TAE from DOV to the end of the feeding artery is performed using coils with or without the combination of liquid embolic agents (**Fig. 1**). In the Yakes type-II AVMs with an aggregate of abnormal arteriovenous communication (classical "nidus"), TAE or DPE is performed mainly using liquid embolic agents. In Cho's type-II or Yakes type-IIIa/IIIb AVMs with single or multiple DOVs, DPE or TVE using coils and/or liquid agents is often performed to close the multiple shunts along the DOV wall. TAE is also considered with liquid agents or large microspheres to decrease arterial inflow or pressure into the AV shunt before DPE or TVE. In Cho's type-IIIa/IIIb AVM with non-dilated or dilated multiple AVFs, TAE or DPE is performed using liquid embolic agents (**Fig. 2**). In the particular Yakes type-IV AVM with innumerable micro-AVFs infiltrating capillary beds, TAE or DPE is performed using 50% diluted ethanol, but the procedure may carry a high risk of ischemic complication than other types (**Fig. 3**) [12].

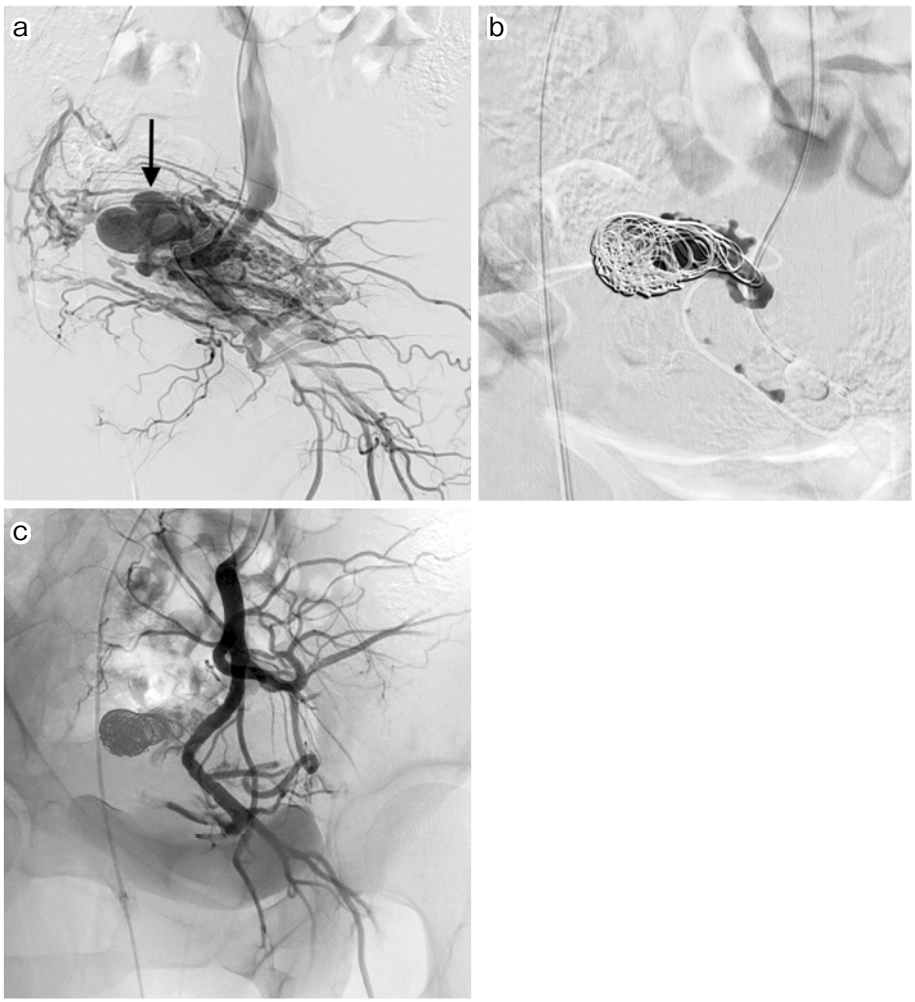

Figure 1. A female in her 50s with Cho's type-I AVM of the left buttock. She suffered from left-buttock pain (Reprinted from Ref. [35]. with permission).
a The left internal iliac arteriogram shows a direct AVF between the distal branch of the internal iliac artery and an aneurysmal dominant outflow vein (DOV) (arrow).
b A 5Fr balloon catheter was placed in the internal iliac artery for arterial inflow control. A microcatheter reached the DOV, and detachable microcoils were deployed as scaffold. 0.7 mL of 20% NBCA-lipiodol mixture was injected into the space among the framing coils in DOV back to the end of the feeding artery.
c Final angiography shows disappearance of the AV shunt.

Embolization Endpoint

The angiographic endpoint is significant flow reduction or disappearance of the AV shunt with delayed visualization of drainage veins. It is important to check if the normal arteries or deep veins are not occluded due to excessive embolization. Intraprocedural ultrasound is also useful for monitoring the reduction of the shunt flow. The longer procedural time may lead to the occurrence of complications, and multi-stage sessions should be considered.

Complications

The incidence and severity of complications depend on the extent or degree of embolization and embolic agents used. Local pain and acute inflammatory swelling almost always occur for several days after the procedure but are manageable by cooling, steroids, or non-steroid anti-inflammatory drugs in most cases. Minor complications include skin blistering or self-healed skin necrosis, transient nerve injury, local infection, and hemoglobinuria. Major complications include skin necrosis requiring surgery, permanent nerve injury, muscle contracture, intraprocedural bleeding from the AVM, and pulmonary embolism from thrombosis of the outflow veins or adjacent deep veins during and after the procedure. Severe adverse events related to excessive usage of ethanol include neurotoxicity, rhabdomyolysis, acute renal failure, and cardiopulmonary collapse. These complications can be prevented by careful patient monitoring and assessment during and after the procedure and by separating multi-stage treatments.

Reported outcomes

Because of the rarity of the disease, large-scale studies re-

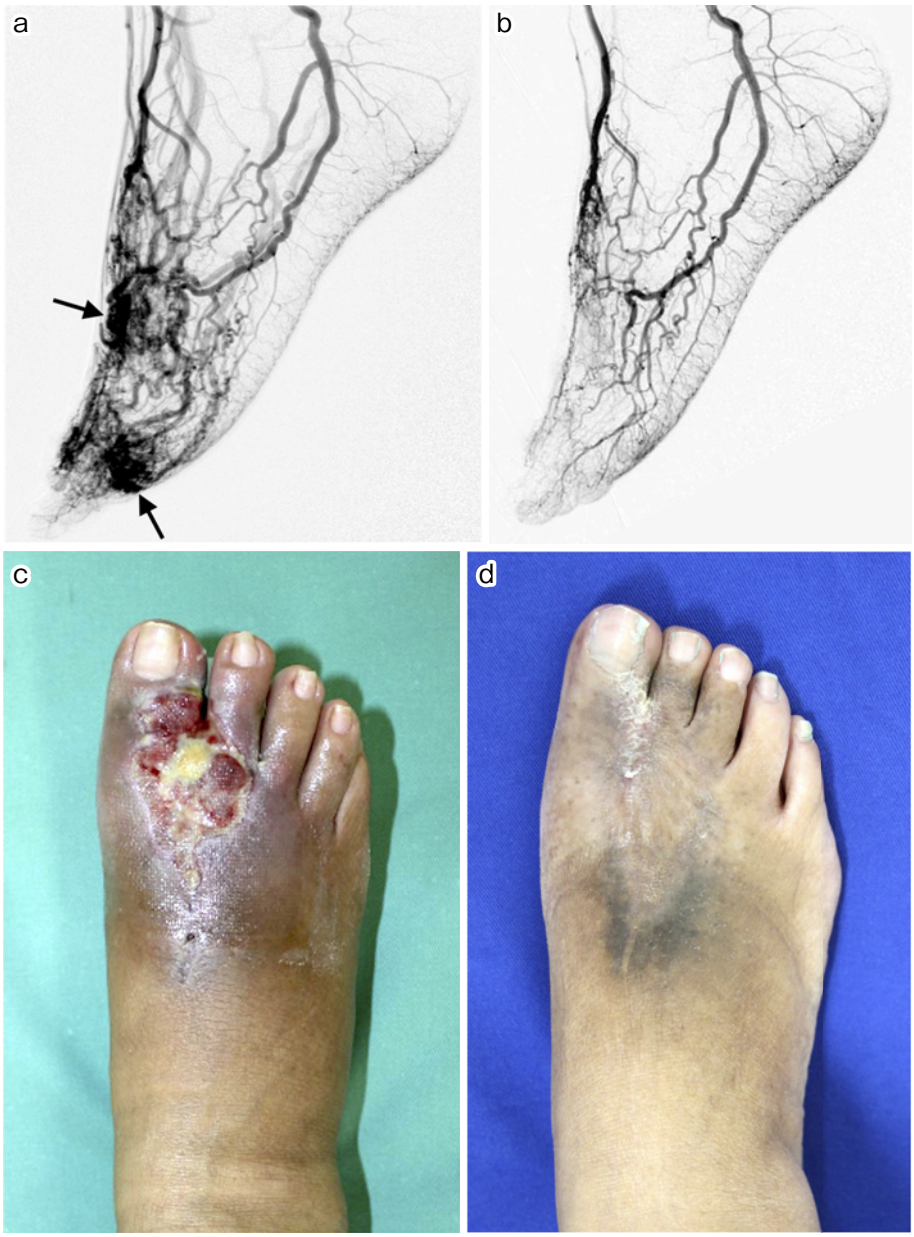

Figure 2. A female in her 40s with Cho's type-IIIa AVM of the left foot.
a The left popliteal arteriogram shows micro-AV shunts both in the dorsal and planter aspects of the foot (arrows). Stepwise direct puncture embolization was performed three times at 4 months intervals. The AV shunt was punctured by 25G needles, and 0.5–1.0 mL of absolute ethanol was injected at 5–10-min intervals under tourniquet control.
b Post-embolization angiography at the third session shows nearly total disappearance of the AV shunt.
c A photograph before embolization. The patient suffered from intractable pain and skin ulcer.
d A photograph 3 years after the last embolization. The skin ulcer was gradually healed.

porting clinical outcomes of embolization for BE-AVMs are limited. Technical outcomes are typically defined as the degree of devascularization at angiography, and 75%-100% devascularization is typically considered as technical success [25, 26]. Clinical outcomes are generally assessed by the combination of clinical response and degree of devascularization: complete remission (CR) = complete resolution of symptoms and signs with 100% devascularization; partial remission (PR) = complete symptom resolution or improvement with 50%-99% devascularization; no remission (NR) = persistent symptoms with <50% devascularization; and failure = symptom aggravation regardless of the degree of devascularization; CR and PR are typically considered as clinical success [8, 27].

Above all, the outcomes of embolization using ethanol as a primary agent have been investigated mainly by the group from Samsung Medical Center in South Korea (**Table. 1**). In 2005, Do et al. first reported the interim results of 175 ses-

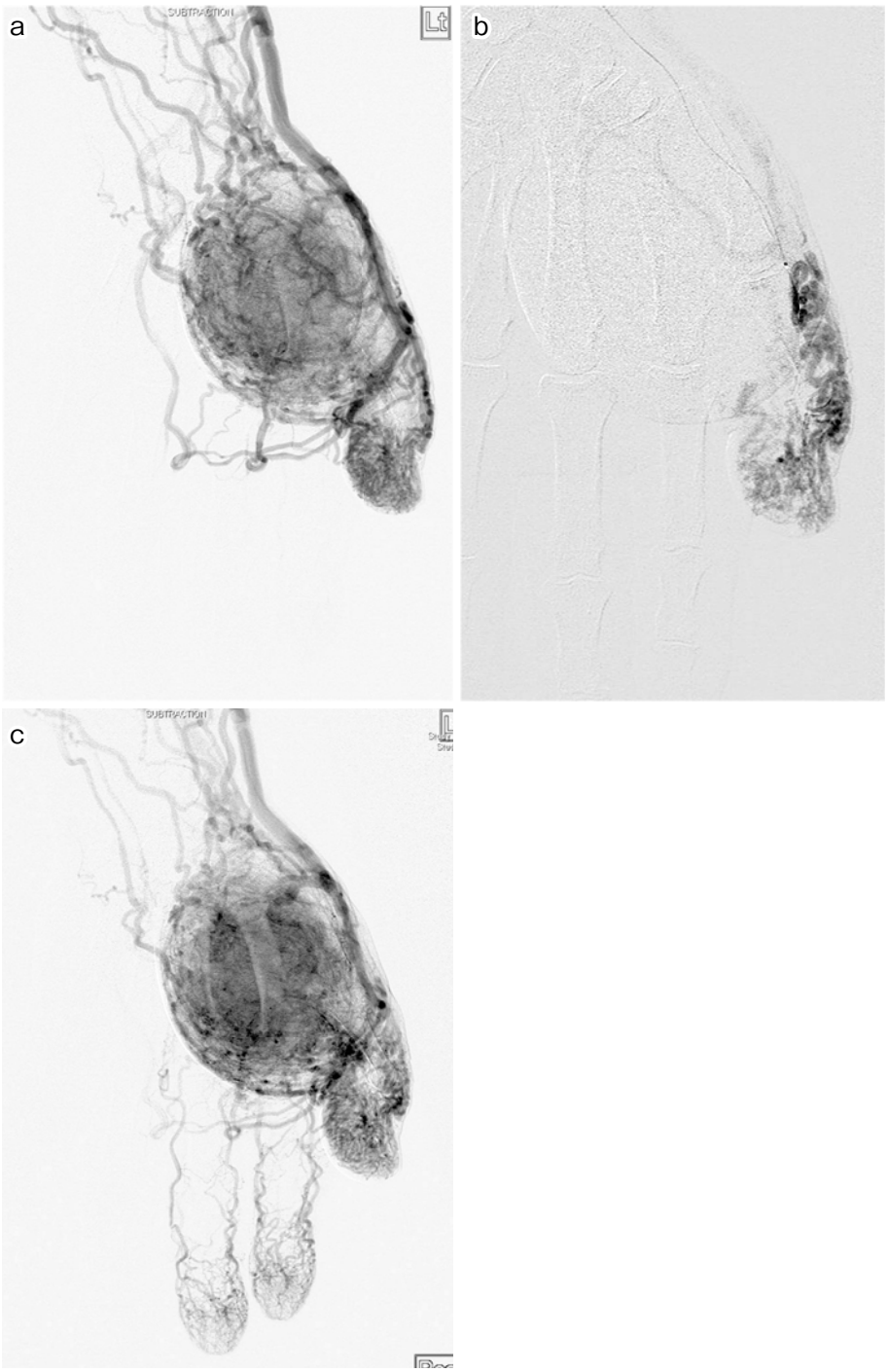

Figure 3. A male in his 60s with Yakes type-IV AVM of the left hand. He suffered from pain, swelling, and deformity of the palm.
a The left radial arteriogram shows diffuse capillary-like stain in the palm and the thumb. Transarterial embolization was performed from each feeding artery using a 1.5Fr flow-guided microcatheter. A total of 7 mL of 50% diluted ethanol was intermittently injected.
b Selective arteriogram of the feeding artery into the thumb shows micro-AV shunts.
c Post-embolization angiography shows mild decrease in the shunt with appearance of the digital arteries in the second and third fingers.

sions of ethanol embolization in 40 patients with BE-AVMs [27]. Although the CR rate was as high as 40%, five (12%) patients had major complications, including infection, acute renal failure due to rhabdomyolysis, permanent median nerve injury, brain infarct, and focal urinary bladder necrosis. In 2006, Cho et al. reported the results of 255 sessions of ethanol embolization in 66 patients and proposed an angiographic classification as described before to analyze the therapeutic outcomes by access routes [8]. Cho's type-II had a higher clinical success rate (100%) than Cho's type-IIIb (83%) and type-IIIa or mixed types (<50%). In 2012, Park et al. also analyzed the results of ethanol embolization in

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Table 1. Reported Outcomes of Embolization Mainly Using Ethanol for BE-AVMs.

Author/year [Ref]	Patient (lesion) number	Mean age (range)	Location	Type of nidus	Procedure number	Approach to nidus	Embolic agents	Clinical results (% of AVM devascularization)	Complications (number)	Follow-up period
Park/2019 [28]	107 (1996-2006)	28	UE (n = 46) LE (n = 35) Trunk (n = 26)	Cho's type: II (n = 27) IIIa (n = 6) IIIb (n = 41) IIIa+IIIb (n = 18) II+IIIa/IIIb (n = 15)	Total 449 Mean 4.2 (1-23)	TA: 196 (44%) DP: 186 (41%) TA+DP: 51 (11%) TA+TV: 16 (4%) (% per total session)	Absolute ethanol: 422 (94%) 50-80% diluted ethanol: 16 (4%) Absolute and diluted ethanol: 11 (2%) Coils: 72 (16%) NBCA: 17 (4%)	CR (100%): 39 (36%) Markedly improved (90-99%): 19 (18%) Improved (50-89%): 24 (22%) NR (<50%): 15 (14%) Failure: 10 (9%) Clinical success: 54% Overall improvement: 77%	Major: 14 (3%) per session Minor: 90 (20%) per session 104 (23% per session, 1% per patient) Skin necrosis (48), skin necrosis and bullae (2), bullae and discoloration (30), nerve injury (13), distal embolism (2), venous thrombosis (4), pulmonary embolism (1), rhabdomyolysis (1), acute pancreatitis (1), gangrene (1), finger contracture (1)	Mean 33 (1-153) mos.
	199 (2007-2017)	33 (p = 0.01*)	UE (n = 64) LE (n = 59) Trunk (n = 66) (p<0.0001*)	Cho's type: I (n = 6) II (n = 57) IIIa (n = 10) IIIb (n = 76) IIIa+IIIb (n = 30) II+IIIa/IIIb (n = 20)	Total 464 Mean 2.3 (1-16) (p<0.0001*)	TA: 142 (31%) DP: 159 (34%) TA+DP: 144 (31%) TA+TV: 19 (4%) (% per total session) (p<0.0001*)	Absolute ethanol: 387 (83%) 50-80% diluted ethanol: 33 (7%) Absolute and diluted ethanol: 44 (10%) (p<0.0001*) Coils: 175 (38%) (p = 0.0003*) NBCA: 29 (6%) (p = 0.27)	CR (100%): 82 (41%) Markedly improved (90-99%): 46 (23%) Improved (50-89%): 46 (23%) NR (<50%): 22 (11%) Failure 3 (2%) Clinical success: 64% (p = 0.10) Overall improvement: 87% (p = 0.014*)	Major: 19 (4%) per session Minor: 86 (19%) per session 105 (23% per session, p = 0.18; 0.5% per patient, p>0.05) Skin necrosis (56), bullae and discoloration (13), nerve injury (20), distal embolism (2), venous thrombosis (4), acute kidney injury (1), acute pancreatitis (1), gangrene (1), bladder rupture (1), bladder neck contracture (1), compartment syndrome (1), focl renal infarction (2)	
Ko/2019 [10]	79 (84)	34 (5-74)	LE (n = 34) Pelvis (n = 22) UE (n = 13) Trunk (n = 11) Kidney (n = 4)	Cho's type: IIa (n = 39) IIb (n = 25) IIc (n = 20)	Total 189 Mean 2.3 (1-12)	TA DP TV	Ethanol Coils Core-removed guidewire	CR (100%): 69 (82%) Markedly improved (90-99%): 7 (8%) Improved (50-89%): 5 (6%) NR (<50%): 1 (1%) Failure 2 (2%) Clinical success: 90% Overall improvement: 96%	Major: compartment syndrome (1), acute pancreatitis (1), arm amputation (1), massive hematuria (1), lymphedema (1) Minor (19): details not available	Mean 37 (1-190) mos.

Table 1. Reported Outcomes of Embolization Mainly Using Ethanol for BE-AVMs. (continued)

Author/year [Ref]	Patient (lesion) number	Mean age (range)	Location	Type of nidus	Procedure number	Approach to nidus	Embolic agents	Clinical results (% of AVM devascularization)	Complications (number)	Follow-up period
Park/2012 [16]	176	29 (1-70)	UE (n = 68) LE (n = 62) Trunk (n = 46)	Cho's type: I (n = 1) II (n = 36) IIIa (n = 6) IIIb (n = 91) Mixed (n = 42)	N/A	TA: 34 (19%) DP: 40 (23%) TA+DP: 83 (47%) TA+DP+TV: 19 (11%) (% per patient)	Ethanol (3-70 mL) NBCA Coils	CR (90-100%): 68 (39%) PR (50-89%): 91 (52%) NR (<50%): 9 (5%) Failure 7 (4%) Clinical success: 90%	Major: skin necrosis (8), skin and tissue necrosis (1), distal arterial embolization (3), permanent nerve injury (1), coil extrusion through the skin (1), coil infection and bacterial endocarditis (1), acute pancreatitis (1), rhabdomiyolysis, and acute renal failure (1) Minor: skin blister (10), skin necrosis (36), skin necrosis with transient nerve palsy (4), transient nerve palsy (8), asymptomatic deep vein thrombosis (2), stiffness in the finger joints (2).	Mean 30 (1-120) mos.
Cho/2006 [8]	66	28 (5-53)	UE (n = 28) LE (n = 26) Pelvis (n = 7) Trunk (n = 5)	Cho's type: II (n = 13) IIIa (n = 2) IIIb (n = 30) II+IIIb (n = 9) IIIa+IIIb (n = 12)	Total 255 Mean 3.9 (1-25)	TA: 141 (51%) DP: 130 (47%) TV: 6 (2%) Multiple: 22 (8%) (% per total approach)	Ethanol Coil	CR (100%): 21 (32%) PR (50-99%): 28 (42%) NR (<50%): 17 (26%) Clinical success: 74%	Major: distal embolism (3), permanent nerve injury (2), infection (2), bladder necrosis (1), brain infarct (1), acute renal failure (1) Minor: skin necrosis (31), bullae (10), transient nerve injury (2)	Mean 17 (0-80) mos.
Do/2005 [27]	40	27 (9-53)	UE (n = 19) Pelvis (n = 50) Trunk (n = 1) LE (n = 16)	N/A	Total 175 Mean 4.4 (1-24)	TA DP TV	Ethanol Coil	CR (100%): 16 (40%) PR (50-99%): 11 (28%) NR (<50%): 7 (18%) Aggravation 1 (2%) Failure 5 (12%) Clinical success: 68%	Major: infection (1), acute renal failure (1), permanent nerve injury (1), brain infarct (1), bladder necrosis (1) Minor: skin blister or necrosis (25), transient nerve injury (2)	Mean 15 (2-48) mos.

Abbreviations: BE-AVM = body and extremity arteriovenous malformations, UE = upper extremity, LE = lower extremity, TA = transarterial, DP = direct puncture, TV = transvenous, CR = complete remission, PR = partial remission, NR = no remission, N/A = not available

*: statistically significant

176 patients with BE-AVMs and found that the localized lesion extent (odds ratio, OR = 0.199) and Cho's types I and II (OR = 0.162) were significant predictive factors for overall clinical response [16]. Furthermore, in 2019, Park et al. chronologically compared the clinical outcomes and complications between two patient groups of BE-AVMs treated with ethanol embolization during the first decade (n = 107, 449 sessions) and the second decade (n = 199, 464 sessions) from 1996 to 2017 [28]. With an increase in treatment experience, the mean number of sessions significantly decreased by 45% from 4.2 to 2.3 ($P < 0.001$), and the single approach by TAE decreased from 44% to 31%, whereas the combined approaches by TAE and DPE increased from 11% to 31% ($P < 0.0001$). The use of diluted ethanol or mixed use of absolute and diluted ethanol increased from 6% to 17% ($P < 0.0001$), and the combined use of coils also increased from 16% to 38% ($P = 0.0003$). The overall improvement rate increased from 77% to 87% ($P = 0.014$), and the treatment failure rate also decreased from 9.3% to 1.5% ($P = 0.04$). They also found that the complication rate was lower with DPE than with other methods ($P < 0.05$) likely due to the reduced ethanol reflux into the normal arteries. The increased use of diluted ethanol reduced skin complications as well as total ethanol dose compared with the use of absolute ethanol. Among Cho's types, the type-IIIa and type-IIIb AVMs had higher complication rates compared with the type-II AVMs (OR = 0.475, $P = 0.013$). These results indicated that the accumulation of treatment experience and the adoption of angiographic classification relevant to the embolization technique improved the therapeutic outcomes and safety.

The outcomes of ethanol embolization for BE-AVMs of the specific locations, including the hand [29, 30], foot [31, 32], and extremity bones [15, 17], have also been reported (**Table. 2**). Park et al. reported the results of 86 sessions of ethanol embolization in 31 patients with hand AVMs with subgroups involving fingers only (n = 14), fingers and palm (n = 9), and palm only (n = 8). AVMs involving fingers only showed significantly higher clinical success rate than those involving both the fingers and palm (93% vs. 38%, $P = 0.0190$) but had no significant difference with AVMs involving the palm only (93% vs. 88%, $P = 1.0000$). However, the complication rates were relatively higher in AVMs involving the fingers only (64%) and fingers and palms (78%) than those without the involvement of fingers (38%) [29]. Hyun et al. reported 61 sessions of ethanol embolization in 29 patients with foot AVMs and found that the lesion extent had a moderate correlation with clinical the success rates ($P < 0.991$; $\rho = 0.633$). AVMs involving <25% of the foot showed better outcomes than those involving >25% (100% vs. 55%), whereas there was no correlation between Cho's type and clinical success ($P > 0.5$; $\rho = 0.143$) [31].

On the other hand, reports are very limited regarding the outcomes of embolization using non-ethanol agents for BE-AVMs (**Table. 3**). White et al. reported the long-term results of embolization using isobutyl cyanoacrylate (IBCA) and NBCA in 20 patients with the extremity AVMs treated from 1982 to 1999 [33]. Of nine patients with lower-extremity AVMs, five were difficult to treat with TAE due to diffuse involvement of all three trifurcation arteries and also required above- or below-the-knee amputation. Of 11 patients with upper-extremity AVMs, symptoms improved in 7 with TAE alone and in the other 4 with resection after TAE. Sofocleous et al. reported the results of 28 sessions of NBCA embolization in 21 patients with AVMs in the hand and forearm. Technical success was achieved in 17 (85%) patients. Symptomatic improvement was obtained in 17 (85%) patients with the mean symptom-free period of 30 months, and no major complication occurred [25]. Tan et al. reported the results of 28 sessions of embolization in 13 patients with extremity AVMs using NBCA alone (n = 7), PVA alone (n = 2), a combination of NBCA and PVA (n = 3), and a combination of NBCA and sodium tetradecyl sulfate (STD) (n = 1). Three (23%) patients were cured, and five (38%) demonstrated improvement. Major complications occurred in two patients: tibial plateau fracture probably unrelated to embolization in one patient with tibial bone AVM and temporary L5 motor loss with foot drop in the other patient with pelvic AVM. Both complications improved conservatively [34]. Kitagawa et al. reported the results of combination of TAE using NBCA and direct puncture sclerotherapy using polidocanol in 23 patients with peripheral AVMs. Of the 23 patients, 17 with upper- or lower-extremity AVMs underwent a total of 23 sessions of the treatment. CR and PR were obtained in 1 (6%) and 14 (82%) patients, respectively. No major complication occurred, but minor complications occurred in two patients, including localized arterial thrombosis and skin ulcer [24]. Wohlgemuth et al. reported short-term results of retrograde transvenous Onyx embolization for 11 patients with Cho's type-II or type-II/IIIb AVMs in BE-AVMs. Preparatory TAE or DPE with Onyx or venous-flow reduction with Amplatzer Vascular Plug were combined as needed. CR and PR were obtained in 8 (73%) and 3 (27%) patients, respectively. No major complications occurred [19]. Osuga et al. reported the results of TAE mainly using superabsorbent polymer microspheres (SAP-MS) in 25 patients with the facial and BE-AVMs [20]. Of 25 patients, 17 showed symptom improvement with TAE alone and 3 with TAE in combination with surgical means. Two patients with finger AVMs underwent amputation of the affected finger, because TAE failed to improve the symptoms. One patient with extensive upper-extremity AVM also underwent amputation at the distal forearm due to aggravation of skin necrosis of the affected hand. In another patient with diffuse infiltrative foot AVM, painful ulcer was not controlled with TAE, but the patient was lost to follow-up. No ischemic complication such as skin necrosis or nerve injury was observed related to TAE with SAP-MS.

Although debates on the choice of embolic agents remain, the reported clinical success rates seem comparable between ethanol embolization (68%-100%) and embolization with non-ethanol agents (62%-100%), but the reports of ethanol embolization tend to show higher incidence of major complications.

Table 2. Reported Outcomes for Embolization Mainly Using Ethanol for the Lesion-Specific Extremity AVMs.

Author/year [Ref]	Patient number	Mean age (range)	Location	Type of nidus	Procedure number	Approach to nidus	Embolic agents	Degree of devascularization	Clinical results	Complications (number)	Follow-up period
Li/2019 [30]	12	35 (12-63)	Hand (n = 12)	Yakes type: IIa (n = 2) IIb (n = 6) IIIa (n = 4)	Total 23 Mean 1.9 (1-3)	DP	Ethanol (3-40 mL) Coils	100%: 7 (58%) 76-99%: 4 (33%) 50-75%: 1 (8%)	CR: 7 (58%) PR: 5 (42%) Clinical success: 100%	Major: none Minor: blistering (12), swelling (12), hemoglobinuria (9), skin necrosis (1)	Mean 37 (14-57) mos.
Park/2011 [29]	31	27 (5-51)	Hand (n = 31)	N/A	Total 86 Mean 2.8 (1-11)	TA: 5 (16%) DP: 6 (19%) TA+DP: 20 (65%) (% per patient)	Ethanol (4-54 mL) Coils	100%: 2 (6%) 76-99%: 19 (63%) 50-75%: 4 (13%) <50%: 6 (19%)	CR: 1 (3%) PR: 22 (73%) NR: 2 (7%) Failure: 5 (17%) Clinical success: 74%	Major: skin necrosis requiring amputation (2) Minor: skin necrosis (12), bullae (7), joint stiffness or contracture (6), transient nerve palsy (4)	Mean 22 (4-60) mos.
Yakes/2016 [32]	3	33 (19-44)	Foot (n = 3)	Yakes type: IIIb (n = 2) IIIb+IV (n = 1)	Total 6 Median 1 (1-4)	DP	Ethanol Coils		CR: 2 (67%) PR: 1 (33%) Clinical success: 100%	Erosion of one coil through the skin removed with surgery (n = 1)	Median 12 (6-12) mos.
Hyun/2013 [31]	29	31 (9-59)	Foot (n = 29)	Cho's type: II (n = 4) IIIa (n = 11) IIIb (n = 9) IIIa+IIIb (n = 2) II+IIIa (n = 1)	Total 61 Median 1 (1-10)	TA: 6 (21%) DP: 11 (38%) TA+DP: 12 (41%) (% per patient)	Ethanol Coils	N/A	CR: 7 (24%) PR: 17 (59%) NR: 3 (10%) Failure: 2 (7%) Clinical success: 83%	Major: skin necrosis (2), toe gangrene (1), pulmonary artery hypertension, arrhythmia, and hypokalemia (1) Minor: skin necrosis (10), skin bullae (8), skin color change (2), transient sensory loss (2), transient nerve palsy (1), superficial or deep vein thrombosis (2)	Median 16 (1-70) mos.
Yang/2020 [17]	12	28 (3-54)	Bones: UE (n = 6) LE (n = 6)	N/A	Total 27 Mean 2 (1-3)	DP	Ethanol (10-45 mL) Coils	N/A	CR: 9 (75%) PR: 3 (25%) Clinical success: 100%	Major: none Minor: hemoglobinuria (8), transient motor nerve injury (1), skin bulla (1)	Mean 24 (6-72) mos.
Do/2010 [15]	22	29 (1-64)	Bones: UE (n = 7) LE (n = 15)	N/A	Total 96 Mean 4.4 (1-12)	TA: 49 (44%) DP: 58 (52%) TV: 4 (4%) (% per total approach)	Ethanol (4-65 mL) Coil	100%: 13 (59%) 76-99%: 4 (18%) 50-75%: 1 (5%) <50%: 4 (18%)	CR: 4 (18%) PR: 14 (64%) NR: 3 (14%) Failure: 1 (4%) Clinical success: 82%	Major; sensory and motor nerve injury (1) Minor; skin necrosis (6), transient nerve palsy (5), bulla (1)	Mean 17 (1-60) mos.

Abbreviations: AVM = arteriovenous malformations, UE = upper extremity, LE = lower extremity, TA = transarterial, DP = direct puncture, TV = transvenous, CR = complete remission, PR = partial remission, NR = no remission, N/A = not available

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Table 3. Reported Outcomes of Embolization Mainly Using Non-Ethanol Agents for Peripheral AVMs.

Author/year [Ref]	Patient number	Mean age (range)	Location	Type of nidus	Procedure number	Approach to nidus	Embolic agents	Degree of devascularization	Clinical results	Complications (number)	Follow-up period
Kitagawa/ 2018 [24]	23	42 (4-74)	HN (n = 6) UE (n = 7) LE (n = 10)	Cho's type: I (n = 2) II (n = 6) IIIa (n = 6) IIIb (n = 9)	Total 29 Mean 1.3 (1-3)	TA DP	NBCA Polidocanol	100%: 2 (9%) 76-99%: 13 (57%) 50-75%: 7 (30%) <50%: 1 (4%)	CR: 2 (9%) PR: 18 (78%) NR: 3 (13%) Clinical success: 87%	Major: none Minor: localized arterial thrombosis (2), skin ulcer (1)	Mean 38 (12-46) mos.
de Beule/ 2016 [18]	22	37 (2-76)	HN (n = 9) Shoulder (n = 4) UE (n = 4) LE (n = 5)	No. of feeders: 1 (n = 9) 2-5 (n = 9) >5 (n = 4)	Total 25 Mean 1.1 (1-2)	TA	Onyx NBCA PVA Microspheres Ethanol	100%: 8 (36%) <100%: 14 (64%)	CR: 9 (41%) PR: 9 (41%) NR: 2 (9%) Clinical success: 82%	Major: skin ulcer requiring excision (1) or amputation (1), peroneal artery occlusion requiring stent placement (1) Minor: pain (6), skin bulla (2), mucosal ulcer (1)	Median 6.5 (1-7) yrs.
Wohlgemuth/ 2015 [19]	11	31 (12-69)	UE (n = 3) Pelvis (n = 2) Buttock (n = 2) LE (n = 4)	Cho's type: II (n = 6) II+IIIb (n = 5)	Total 23 Mean 2.1 (1-3)	TA DP TV	Onyx (4-48mL) AVP	100%: 10 (91%) 95%: 1 (9%)	CR: 8 (73%) PR: 3 (27%) Clinical success: 100%	Major: none Minor: pain and swelling (n = 1)	Mean 8 (1-14) mos.
Tan/ 2004 [34]	13	34 (21-63)	UE (n = 4) LE (n = 9)	N/A	Total 27 Mean 2.1 (1-5)	TA DP	NBCA PVA STS Coil	N/A	CR: 3 (23%) PR: 5 (38%) NR: 5 (38%) Clinical success: 62%	Major: Tibial plateau compression fracture (1), temporary L5 neuropathy (1)	Median 3.0 (1.0-12) yrs.
Osuga/ 2002 [20]	25	32 (12-66)	Face (n = 5) UE (n = 8) LE (n = 12)	N/A	TAE 72 Mean 2.8 (1-11) DPE 12 Mean 2.4 (1-3)	TA DP	SAP-MS NBCA Coils Polidocanol Ethanol	N/A	Improved with TAE alone: 17 (68%) Improved with TAE combined with surgery: 3 (12%) Complete surgical removal after TAE: 3 (12%) Failure: 2 (8%)	Mucosal necrosis by DPE with ethanol (1)	Mean 38 (7-110) mos.
Sofocleous/ 2001 [25]	21	26 (11-51)	UE (n = 21)	N/A	Total 28 Mean 1.3 (0-3)	TA	NBCA PVA Ethanol	75-100%: 17 (85%)	Improved: 17 (85%)	No complications necessitaing therpy	Median 24 (0.5-78) mos.
White/ 2000 [33]	20	32 (13-68)	UE (n = 11) LE (n = 9)	N/A	Total 40 Mean 2.2 (1-6)	TA	IBCA NBCA	N/A	Improved by TAE alone (5) Improved by TAE combined with resection (6) Required AKA (1) and BKA (4), but walking well with prosthesis Required toe (1) and finger (2) amputation, butimproved Required graft, but improved (1)	NBCA migration in the lung (1), digital spasm by nontarget embolization (1)	Median 7.9 (1-18) yrs.

Abbreviations: AVM = arteriovenous malformations, HN = head and neck, UE = upper extremity, LE = lower extremity, TA (E) = transarterial (embolization), DP (E) = direct puncture (embolization), TV = transvenous, NBCA = n-butyl cyanoacrylate, IBCA = isobutyl cyanoacrylate, PVA = polyvinyl alcohol, STS = sodium tetradecyl sulfate, SAP-MS = superabsorbent polymer microspheres, CR = complete remission, PR = partial remission, NR = no remission, AKA = above-the-knee amputation, BKA = below-the-knee amputation, N/A = not available

Summary

Embolization remains the mainstay in the management of symptomatic BE-AVMs as a minimally invasive and function-preserving option. The goal of embolization is to obliterate the AV shunt to reduce symptom, and the access routes and choice of embolic agents should be based on the individual angioarchitecture of the AVM. As BE-AVMs are often difficult to "cure" with a procedural risk of severe complications, multi-stage sessions are preferred to improve safety and control the symptoms, especially for large and complex BE-AVMs. BE-AVMs also tend to recur, and additional treatment may be required in the long-term period. Therefore, patients should be managed by a dedicated multidisciplinary team to discuss about appropriate therapeutic options on a case-by-case basis.

Conflict of Interest: None

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