Chapter

Advocating Intraluminal Radiation Therapy in Cerebral Arteriovenous Malformation Treatment

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Abstract

In 2014, ARUBA (a randomized trial on cerebral Arteriovenous Malformation – AVM) found patients treated using prevalent interventional strategies are three times more likely to suffer a stroke/die compared with those treated conservatively (blood pressure reduction). Subsequent controversy led the European societies dealing with AVM to organize a consensus conference. Among the statements made was: "There **may** be indications for treating patients with higher Spetzler-Martin (SM) grades, based on a case-to-case consensus decision of the experienced team". Thus, a clear accord emerges. There is a lacuna/weakness of interventional modalities when addressing high SM grade AVMs. This lack of a clear treatment choice originated our review. We attempt to identify the advantages and challenges of each present treatment/evaluation modality and highlight core requirements for future strategies. We conclude that existing modalities provide substantial recent improvements, yet the core challenge persists. Finally, we advocate testing a novel modality – intraluminal radiotherapy (active implants) by exploiting the "candy wrapper" or edge effect. If proven effective, this approach could offer gradual vessel occlusion with minimal abrupt hemodynamic changes known to induce hemorrhage, the lowest recurring session number (reduced costs), minimally invasive attributes and very low radiation (dose/dose rate) kinetics minimizing potential Adverse Radiation Effects (AREs).

Keywords: arteriovenous malformation, hemorrhage, embolization, radiosurgery, gamma knife, surgical resection, intraluminal radiation therapy

1. Introduction

AVM is a tangled web of blood vessels, in which arteries directly transition into veins without intermediate microcirculation elements that provide perfusion to surrounding tissue. The AVM blood vessels are called a nidus and have little resistance to flow compared with a normal capillary bed. Such structure manifests violent flows which result in increased hemorrhage risks. Due to growing use of advanced imaging modalities, there has been increased incidental detection of cerebral AVMs. When detected, there is impending need for treatment since stroke

chance for an unruptured and untreated AVM is ~20–40% per decade [1]. About 38–71% of patients presenting brain AVM suffer intracranial hemorrhage [2]. Given these statistics, interventional treatment appears vital. Currently, three prevalent modalities exist: endovascular embolization, stereotactic radiosurgery (SRS), and surgical resection. Each modality conveys a wide risk array (safety/efficacy). Thus, many AVMs ultimately remain untreated (see further data below). Unfortunately, these are typically the larger AVMs that could better benefit from intervention (~76% of AVMs having a nidus <30 mm are treated; compared with ~57% of those having a nidus of 30–59 mm and only ~14% of those having a nidus >60 mm) [3]. Moreover, embolization typically necessitates a series of interventional procedures/sessions (up to 11, on average 2.6) [4]. Each procedure involves patient hospitalization, advanced imaging, general anesthesia, and a high-risk operation but, most importantly, exhibits a 3.2% chance of significant complications [4]. Finally, due to a low obliteration likelihood (11–40%), embolization is not recommended as a single-modality therapy and is usually combined with radiosurgery. Radiosurgery (if successful) takes 1–3 years to achieve obliteration. Thus, patients remain at hemorrhage risk for a lengthy treatment period [5]. To conclude, many patients with cerebral AVM benefit less from current prevalent treatment modalities that carry high risks, costs, and intensive procedures and, even if eventually effective, take years to complete. In 2014, the largest randomized trial on AVMs (ARUBA trial) found that patients treated using the prevalent interventional strategies were three times more likely to suffer a stroke or die compared with those treated only for blood pressure reduction [6]. ARUBA elicited a plethora of reactions. Some were relatively supportive, but many more criticized the study methods and outcomes. Eventually, the controversy led the European societies dealing with AVM to organize a consensus conference. A clear accord emerges. There is, indeed, a lacuna or at least weakness of interventional modalities when addressing high SM grade AVMs. The lack of clear treatment choice for a pathology with a point prevalence of ~18/100,000 in adults responsible for 4% of all primary intracerebral hemorrhages is the motivation for this review [7].

1.1 Definitions and angioarchitecture

AVM features a vascular region lacking transition hierarchy, where arteries change directly into veins (**Figure 1**) [13]. AVM physical appearance is a well-defined enclosed volume of entangled blood vessels mostly known as a "nidus." Arteries entering the nidus are termed "feeding arteries" and veins leaving it are termed "draining veins" (**Figure 2**) [9].

AVMs may appear in virtually every vascular body region. Clinically, significant AVMs are mainly classified as CNS (cerebral), pulmonary, abdominal, renal,

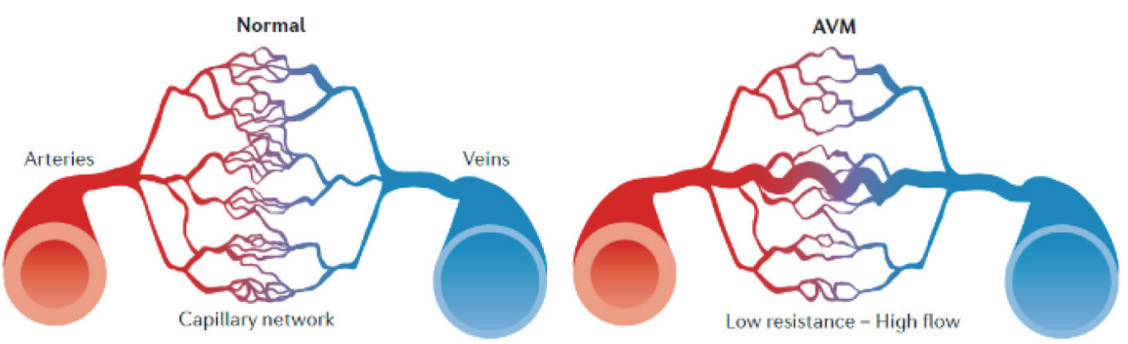

Figure 1.
AVM angioarchitecture [9].

hepatic, and peripheral [8–16]. This chapter focuses on cerebral AVMs due to the high risks and challenging treatment involved with this class. Nidus sizes vary in diameter between 1 and 10 cm. AVMs <3 cm are classified as "small." AVMs between 3 and 6 cm are classified as "medium." AVMs >6 cm are considered as "large" [8]. The majority of AVMs are medium sized (~55%), followed by small (~38%) and then large (~7%) [17, 18]. The nidus structure does not typically obstruct blood flow; in fact, the opposite is true (see below). Thus, the organ function is usually preserved. However, in rare cases (especially large AVMs), the nidus is orientated or structured in a way that impedes perfusion (steal phenomena) [9]. Here, clinical features of ischemia or lack of brain function may be present [17].

1.2 Pathophysiology

AVMs are considered as a major cause of intracerebral hemorrhage, particularly in the young population (33.5% for age<20years) [19]. From a fluid mechanics perspective, arterioles constitute the main flow resistance/drop of the vascular tree (**Figure 3**, OpenStax CNX) via a mechanism of rapid increase of surface contact between the blood and the endothelial surface and thus shear stress induction. Lack of arterioles causes minor pressure drops across the nidus. The mean arterial blood pressure difference between normal and AVM cases is ~40 mmHg

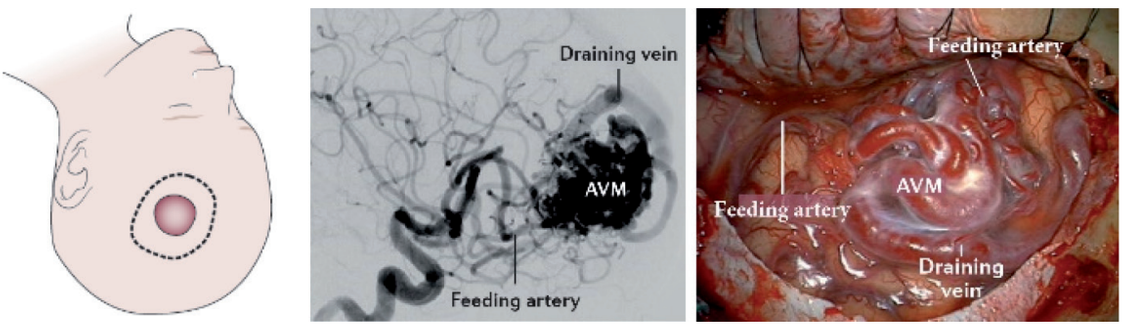

Figure 2.
AVM nidus. Physical location (left), angiogram (center), and pre-surgical anatomy (right) [9].

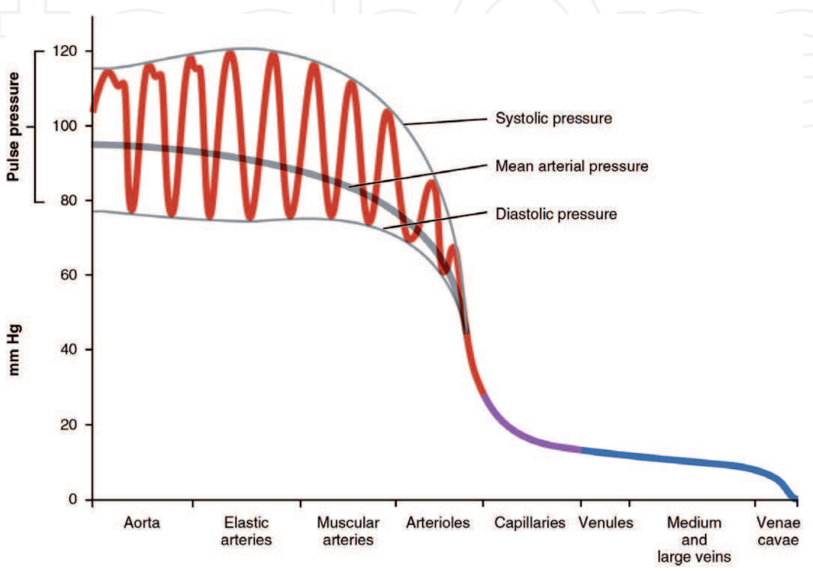

Figure 3.
Pressure drop along the vascular tree.

and has become an indicator for potential hemorrhages [20]. These findings are confirmed by modern 4D flow magnetic resonance imaging (MRI) and high-resolution magnetic resonance angiography (HR 3D MRA) [21, 22]. The CNS vascular network is not equipped to endure pressure drops exceeding 10 mmHg, particularly not the structurally thin veins. Thus, the biomechanical aspects of AVM pressures, flows, and shear stresses play a major part in the structural failure of its vessels' vascular walls.

1.3 Pathogenesis

AVM is generally considered congenital and/or of developmental origin. Beneš and Bradác describe several genetic pathways associated with AVM pathogenesis, such as hereditary hemorrhagic telangiectasia (HHT, an autosomal dominant genetic disease) [23]. Typically, the genes Endoglin, ALK-1 (ACVRL1, TGF-β related), and SMAD4 are implicated [24]. These genes also participate in angiogenesis and vascular remodeling. The main signaling pathways disrupted are: (i) TGF-β—cellular growth, communication, and inflammatory processes; (ii) NOTCH—angiogenesis, considered critical for arterial fate determination; (iii) MAPK(1/3)—physiological and pathological cell proliferation; and (iv) PI3K/Akt—cell cycle regulation.

1.4 Epidemiology, natural history, and clinical features

Fast-flow lesions' prevalence is estimated to be 1–2 out of 10,000 people or 1.2–1.3 in 100,000 per person-year [23]. AVMs are found in 0.05% of all brain MRIs [25]. In the USA and Canada, 5000 new cases are detected yearly [26]. Demographic, morphological, and clinical (particularly age-related) characteristics do vary, but many important pathology-related statistics (e.g., rate of incident hemorrhages) remain roughly similar worldwide [17]. In South Africa, male gender and African-black origin were found to be strong indicators for AVM seizure development [27]. Frontal (20.4%), parietal (22.2%), temporal (16.6%), and cerebellar (14.0%) are the most common anatomical brain regions to present AVMs [17, 27]. Supratentorial lesions account for 90% of brain AVMs [28]. Intracranial hemorrhage is the most common clinical presentation (30–82% of lesions) [29]. AVMs account for 1–2% of all strokes and 2–4% of all non-traumatic intracerebral hemorrhages [23]. However, the unique age distribution among stroke etiologies (the median age for an AVM patient is 32 years old [30]) suggests that AVMs are responsible for more than a third of hemorrhagic strokes in young adults [19]. Furthermore, some studies suggest that higher hemorrhage risk values of 4.6% [31] and 30% of lesions are subarachnoid [32]. These are considered highly catastrophic and present the mortality rates of 25–50% [33]. Main factors influencing hemorrhage risk statistics are initial hemorrhagic (7.48%) or seizure (4.16%) presentations, associated aneurysms (6.93%), and deep venous drainage (5.42%) [31]. Other clinical representations are neurological deficits (24%), chronic headaches (19%), and focal or generalized seizures (46%) [17]. The American Association of Neurological Surgeons (AANS) provides a wide symptoms list—seizures, muscle weakness or paralysis, loss of coordination, difficulties carrying out organizational tasks, dizziness, headaches, visual disturbances, language problems, abnormal sensations, memory deficits, mental confusion, hallucinations, and dementia [34]. Annual mortality rates vary between 0.7 and 2.9% [23]. Considering an estimated number of 300,000 US patients, this results in ~2100–8700 annual mortalities in the USA alone.

1.5 Brief history

Early AVM descriptions may date back to ~1500 BC, evidenced in the Ebers Papyrus description of hemorrhoids, varicose veins, and aneurysms. Vessel malformations were apparently also familiar throughout the Roman and early Arabic empires. However, the first modern documented AVM procedure was performed by Hunter during the eighteenth century, the first official clinical diagnosis was described in 1895, and the first surgery (a feeding artery ligation) was performed by Giordano in 1889 and was immediately followed by a full AVM resection in Paris [23]. The early era of AVM microsurgery is traditionally attributed to Kunc et al. who suggested the whole AVM obliteration as a standalone fully efficient treatment strategy in 1965 [35]. The interventional radiology approach and radio-surgical techniques emerged during the 1980s and eventually paved the way for present treatment modalities. The 1980s were also pivotal regarding treatment strategies. Up to then, recommendations for AVM treatment were mainly institution/physician based. However, during the 1980s, Spetzler and Martin (based on vast surgical work) developed the first well-established AVM classification and treatment scale. This grading scale is considered the "gold standard" decision-making tool in the field to date [36].

2. Main diagnosis and imaging tools

Though AVM prevalence is estimated to reach up to 0.2% of the population, actual confirmed diagnosis rate is only ~0.02% [23, 37]. This significant gap is attributed to the fact that AVMs are congenital pathologies remaining generally mildly symptomatic until clinical presentation appears (unfortunately, this is typically hemorrhagic stroke) [23]. AVMs are mostly diagnosed and confirmed using radiology. The imaging findings also greatly influence treatment evaluations. Two strict AVM diagnostic criteria are: indication of a nidus and clear venous drainage [38]. Angiographic elements evaluated as indications for AVMs' clinical significance, and risk assessments include: arterial supply and venous drainage identification, nidus position, geometry, and size, presence of intracranial hemorrhage, and related pathologies [39]. The presence of aneurysms is associated with 26% of AVM patients [27].

2.1 Digital subtraction angiography

DSA is a vascular mapping technique based on conventional angiography. DSA involves an additional pre-processing step that removes non-vascular anatomical data [40]. Angiography is the gold standard methodology for the characterization and delineation of cerebral AVMs and in the evaluation of cerebrovascular diseases [41, 42]. The method dynamically displays vascular transitions and is uniquely able to delineate the size and number of feeding arteries and their origins, measure the nidus size and compactness, and evaluate venous drainage locations [42]. In addition to its significant diagnostic role, angiography is the main technique used by interventional radiologists to accurately navigate through the neurovascular environment and assess treatment progression and related events through interventional sessions [43, 44]. DSA is performed using selective (the catheter used for contrast administration is only advanced to the AVM vicinity) or super-selective (the catheter is further advanced to the AVM feeding arteries) approaches [23]. DSA is increasingly being supplanted by the less invasive computed tomography angiography (CTA) and the X-ray and nephrotoxic contrast-devoid MRA.

2.2 Computed tomography

CT comprises a limited diagnostic tool for unruptured AVMs [45]. Lower density areas may (potentially) indicate the AVM in CT scans [46]. The great contribution of CT scanning in AVM diagnosis lies in its high sensitivity for acute bleeding detection, which makes it a front-end diagnostic tool when patients present acute symptoms related to the pathology [47]. CT is also used to assess efficacy and complications of embolization interventional treatments [47].

2.3 Computed tomography angiography

CTA combines the CT imaging procedure with contrast agent injection. This enables real-time (RT) structural presentation of neurovascular angioarchitecture (e.g., nidus, arterial feeders, and draining veins) and identifying associated pathologies such as fistulas and aneurysms [38]. Gupta et al. demonstrated that it is even possible to obtain good quality intranidal angiograms using RT CTA for anatomic localization of a specific catheterized (embolized) AVM region [48].

2.4 Magnetic resonance imaging

Smith et al. found MRI which is superior to CT and angiography in determining nidus size and location, detecting AVM effects on adjacent brain tissue, and showing the obliteration extent following embolization [49]. MRI also facilitates AVM classification into base categories (e.g., sulcal/gyral) [23]. Use of flow turbulence and velocities as benchmarks has been shown to increase MRI diagnosis efficacy [23, 50]. MRI is considered highly efficient in detecting and delineating hemorrhagic episodes [23]. In addition, it can detect damage and atrophies in surrounding brain tissue and related pathologies such as aneurysms and fistulas. The latter are considered challenging for early detection and feature high annual risks for hemorrhagic events (7.5%) [41].

2.5 Functional MRI

fMRI is used to detect abnormalities in brain areas adjacent to AVM borders or deficits in specific cognitive tasks correlated with regions affected by it [41]. fMRI can help to evaluate AVM margins and aid in preventing damage to surrounding brain tissue during interventional sessions. AVMs are congenital pathologies. Thus, it is suggested that the developing brain neuroplasticity will present different fMRI images for healthy and pathologic cases. Caramia et al. used fMRI and transcranial magnetic stimulation (TMS)—which directly explore cortical neurons' electrical activity—and showed cortical motor areas reorganized in the AVM containing hemisphere [51]. The main limitation of fMRI is that it does not directly detect AVMs as MRI does. Therefore, it should be used as a treatment planning tool rather than for standard diagnostics [23].

2.6 Magnetic resonance angiography

MRA is valuable in providing AVMs with 3D angiographic images and hemodynamic data [23]. MRA techniques are characterized by two main parameters—flow and contrast. State-of-the-art MRA techniques are:

- Time-of-flight (TOF) MRA: TOF-MRA or inflow angiography enhances blood flow areas by shortening the MRI echo time (TE) parameter, thus reducing the

execution number in each flow-related voxel in comparison with stationary voxels. This results in flow patterns appearing brighter. The technique can also aid in finding residual AVMs [41]. However, Lee et al. report the accuracy and specificity rates of only 75–78 and 68% respectively, which leaves DSA at the front-end [52].

- Phase contrast (PC) MRA (**Figure 4**): In PC-MRA, phase shift differences between stationary tissue and flowing blood results from the application of a bipolar phase-encoding gradient and a velocity-encoding factor [23]. Since phase change is coupled with velocity vectors, the technique is considered superior to TOF-MRA (better detecting flow directions, minor velocity changes, and slow regions). Chang et al. used PC-MRA post-processing computational fluid dynamics to calculate shear stresses at vascular walls [22]. Wu et al. used PC-MRA to identify peak flows, velocities, and their exact location within the nidus and feeders [53]. To conclude, PC-MRA is a promising technology but is still not comparable with conventional angiography [23].

- Time-resolved imaging of contrast kinetics (TRICKS) MRA: Here, continuous imaging is employed during the passage of a contrast agent yielding a movie with an acquisition rate of up to three frames per second [41]. These improvements enable the visualization and calculation of flow through regions of the AVM (also selectively), enabling confirmation of suspected findings on conventional imaging tools [41]. The technique findings correlate well with DSA with regard to nidus size and location, venous drainage pattern, and arterial feeders in multiple studies but still lag DSA in spatial and temporal resolutions.

2.7 Diffusion-weighted MRI

These methods are based on the diffusive anisotropy of water molecules along nerve axons and plexus, where axial motion takes precedence [41, 54]. Here, we can find techniques such as diffusion tensor imaging (DTI), diffusion spectrum imaging (DSI), and high angular resolution diffusion imaging (HARDI). These more recent techniques serve as a valuable non-invasive pre-operative and pre-radiosurgery tool to evaluate the involvement and proximity of cerebral AVMs to white matter tracts [41]. Using these methods, it provides clinicians with strong risk assessment capabilities, particularly regarding the microsurgery approach and track planning [55]. dwMRI can be used with other technologies for presenting a combined vascular and neuroanatomical image [55]. It might also enable very early identification of ischemic areas [46]. dwMRI is limited mainly to white matter tracts and presents high sensitivity to protocol operation parameters (e.g., TR/TE/spatial resolution) and artifacts from inadvertent sources.

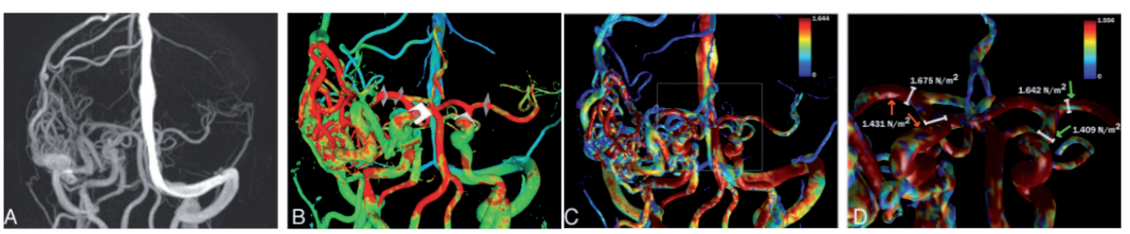

Figure 4.
(A) PC-MRA original image of right temporal AVM, with (B) velocity, (C) whole brain, and (D) feeding arteries shear stresses data [22].

2.8 Summary

AVM analysis is based on the findings of multiple modalities—vascular anatomy of nidus and feeders, acute/chronic brain matter pathological presentations, flow and velocity rates, and surrounding tissue anatomical and functional attributes (e.g., connectometractography). Each modality presents specific strengths and weaknesses. CT is extremely sensitive to hematomas and offers several AVM anatomical finding capabilities. CTA is used to diagnose AVM in patients with acute hematomas. MRI presents improved topography and the detection of subacute and chronic hematomas and surrounding brain tissue pathologies. PC-MRA is used for high-resolution vascular imaging and provides biomechanical data (e.g., shear stresses), that is, highly beneficial in clinical assessment. Functional-anatomical relations data are effectively gathered using fMRI and dwMRI which provide strong clinical decision-making tools. Finally, DSA remains the gold standard for both diagnostic and procedural purposes due to its high-resolution real-time imaging of cerebral angioarchitecture. To conclude, brain imaging is a prolific field constantly presenting the development of promising improved and new modalities.

3. Grading and classification

3.1 The SM grading system

In 1986, Spetzler and Martin published a relatively simple AVM classification system called "SM Grading" [36]. SM is considered as the gold standard to date. The system requires three parameters, evaluated using angiography, CT, and MRI (**Table 1**): size, venous drainage pattern ("superficial" if all drainage is via cortical veins and "deep" if some or all drainage is via deep veins), and neurological eloquence of adjacent brain regions ("eloquent" regions are those well-defined by a neurological function, while the regions of less defined function or disabling effects when disrupted such as temporal lobes and cerebellar cortex are considered "non-eloquent"). SM eventually sorts AVMs into five grades. Inoperable AVMs are considered grade six. Spetzler and Martin correlated their grading with the surgical outcomes of 100 patients and found it to be well-correlated with both minor and major post-operative neurological deficits. Further validations were later performed by both the authors and peers [56].

3.2 Modifications of SM

Several modifications of the SM grading system have been suggested over the years. Following are some key examples. De Olivera et al. suggested including

Graded feature	AVM size (cm)			Eloquence of adjacent brain		Pattern of venous drainage	
	Small (<3)	Medium (3–6)	Large (>6)	Non-eloquent	Eloquent	Superficial	Deep
Points assigned	1	2	3	0	1	0	1

Grade = [size] + [eloquence] + [venous drainage]; that is (1, 2, or 3) + (0 or 1) + (0 or 1).

Table 1.
Determination of AVM grade [36].

two Grade 3 subgroups with different patient management [57]: 3a (large size, pre-operative endovascular embolization followed by microsurgical resection) and 3b (venous drainage and/or eloquence, generally treated with radiosurgery). They found their modified classification a useful guide for the best treatment but indicated that it has many exceptions. Lawton et al. suggested further subcategorizing Grade 3 AVMs into four classes for better correlating the SM grading with associated surgical risks (– less risk, + more risk) [58]: Grade 3–AVMs (small nidus size, deep venous drainage, and eloquent adjacent brain tissue) have a surgical risk similar to that of low grade AVMs and can be safely treated with microsurgical resection, Grade 3+ AVMs (medium size, superficial drainage, and eloquent) have a surgical risk similar to that of high-grade AVMs and are best managed conservatively. Grade 3 AVMs (medium, deep, and non-eloquent) have intermediate surgical risks and require judicious selection for surgery. Grade 3* AVMs (large, superficial, and non-eloquent) are either exceedingly rare, with a surgical risk that is unclear, or theoretical lesions with no clinical relevance. Finally, fairly recently in 2016, Neidert et al. suggested a grading system for patients with ruptured AVM-related IntraCerebral Hemorrhage (AVICH) to predict clinical outcome [59]. Their system extended SM with parameters such as age, diffuse nidus (from the Lawton-Young grading system, that added patient age, hemorrhagic presentation, nidal diffuseness, and deep perforating artery supply in 2010 to improve neurological outcome prediction and refine patient selection [60]), intracerebral hemorrhage volume (30 CC threshold), and intraventricular hemorrhage (derived from the intracerebral hemorrhage score). They demonstrated that their score predicts the outcome of patients with ruptured AVM and associated ICH better than previous grading systems (SM included). They cautioned that an external validation is needed before this score is tested in a prospective multicenter cohort. To date, no modified grading system has become as well-established as the SM grading.

3.3 SRS grading scales

Schwartz et al. tried to predict the AVM obliteration success of single-dose photon SRS for individual patients [61]. They defined the obliteration prediction index (OPI ≡ marginal dose of radiation given at the edge of the target lesion in gray/lesion diameter in centimeters). They concluded that the exponential function $P = 1 - A e^{-B \cdot OPI}$ (where P is the obliteration probability and A, B are constants) is well-correlated with successive chance, partly describes the biological effect of radiation, and is independent of the device (marginal dose) used. They suggested that radiosurgery centers use this model to facilitate successful treatment prediction.

Pollock-Flickinger developed a grading system to predict excellent patient outcome (complete AVM obliteration without any new neurological deficit) following single session AVM radiosurgery [62]:

$$\begin{aligned} \mathrm{AVM}_{\mathrm{score}} = {} & 0.1\ \mathrm{AVM}_{\mathrm{volume}}[\mathrm{cm}^3] + 0.02\ \mathrm{Patient\ age}\ [\mathrm{years}] \\ & + 0.3\ \mathrm{AVM}^{*}_{\mathrm{location}} \end{aligned} \tag{1}$$

where * indicates: frontal or temporal = 0; parietal, occipital, intraventricular, corpus callosum, or cerebellar = 1; basal ganglia, thalamic, or brainstem = 2.

They concluded that their proposed AVM grading system strongly correlates ($R^2 = 0.88$) with patient outcomes but cautioned that further testing by independent centers using prospective methodology is still required.

In 2016, Pollock et al. compared five AVM grading scales—SM, radiosurgery-based AVM score (RBAS), Heidelberg score, Virginia Radiosurgery AVM Scale (VRAS), and proton radiosurgery AVM scale (PRAS)—at predicting SRS outcomes

Grading scale and year	Variables						Type of scale (range)
	Size	Vol	Patient age (years)	Location	Venous drainage	Presentation	
SM, 1986	6 cm = III	NA	NA	Non-eloquent = 0 eloquent = 1*	No = 0 yes = 1	NA	Integer-based (1–5)
Modified RBAS, 2008	NA	0.1× vol in ml	0.02×age	0.5× (not deep = 0, deep = 1)†	NA	NA	Continuous
HS, 2012	<3 cm or ≥3 cm	NA	≤50 or >50	NA	NA	NA	Integer-based (1–3)‡
VRAS, 2013	NA	4 cm^3 = 2	NA	Non-eloquent = 0; eloquent = 1*	NA	No bleed = 0 bleed = 1	Integer-based (0–4)
PRAS, 2014	NA	0.26× vol in ml	NA	0.7× (not deep = 0, deep = 1)†	NA	NA	Continuous

*HS, Heidelberg score; NA, not applicable.*Eloquent location is defined as sensorimotor, language, or visual cortex, hypothalamus, thalamus, brain stem, cerebellar nuclei, or regions directly adjacent to these structures.*

†*Deep location is defined as basal ganglia, thalamus, or brainstem.*

‡*Heidelberg score: 1 = (<3 cm and ≤ 50 years), 2 = (either <3 cm or ≤50 years), and 3 = (≥3 cm and>50 years).*

Table 2.
AVM grading scales [63].

AVM feature		Points
Number of feeding vessels	<3	1
	3–5	2
	≥6	3
Eloquence of adjacent areas	Non-eloquent	0
	Eloquent	1
Presence of AVF[a]	No AVF	0
	AVF	1

[a] *AVF = arteriovenous fistula or fistulous component.*

Table 3.
Classification scheme for risk assessment during embolization procedures for brain AVMs [64].

(**Table 2**) [63]. Their criterion was AVM obliteration without a decline in modified Rankin Scale (mRS) score (excellent outcome). They concluded that continuous scores AVM grading scales (RBAS and PRAS) outperformed integer-based grading systems in the prediction of AVM obliteration outcomes since they directly correlate with patients' existing physical attributes.

3.4 Grading systems for embolization

Even though endovascular embolization widely differs from surgical or SRS approaches, dedicated grading was not considered as a broad/general tool until fairly recently. In 2010, Feliciano et al. conducted an extensive literature survey and correlated endovascular treatment with AVM characteristics. Points were given according to feeding vessels, eloquence, and fistulae presence (**Table 3**) [64]. They concluded that a grading scale similar to SM for use in risk assessment and outcome determination in brain AVM patients treated by endovascular techniques seems adequate and clinically feasible.

3.5 Summary

Though posited in 1986, the SM AVM grading system remains the gold standard in predicting surgical treatment success. The development and assimilation of SRS led to uniquely dedicated grading. The future probably lies with "continuous" grading, where scores are directly correlated with AVM and patients' actual features and properties. Endovascular dedicated grading has just recently emerged, mostly based on large literature surveys and meta-analyses, but apparently shows real promise (though it still necessitates firmer actual validation).

4. Embolization

Embolization is intended to physically block blood flow to the AVM. It is a minimally invasive endovascular procedure carried out by an interventional radiologist. AVM embolization is considered among the most challenging in the field due to the vasculature target tortuous hemodynamic formation but, more so, due to its high-pressure arteries directly connecting with low-pressure veins (AV shunts). If arteries are proximally occluded, anastomoses develop from nearby vessels creating new shunts. Thus, proximal arterial occlusion has no curative effect and is restricted to pre-surgical situations [23]. In contrast, direct AVM treatment requires

distal (transarterial) embolization. First, navigation is performed all the way to the venous section. Then, an embolic agent is super-selectively introduced into the draining veins via microcatheters that are retracted backwards as the vasculature fills up (all the way to the arterial feeders). Vessel selection tract is traditionally based on DSA.

In 1995, Frizzel et al. reviewed the cure, morbidity, and mortality associated with the embolization of 1246 brain AVMs during the previous 35 years [65]. Cure rates were 4–5%. Temporary and permanent morbidities were 10 and 8–9%, respectively. Mortality was 1–2%. These statistics improved over the years. However, to date, embolization is generally considered a pre-operative (pre-SRS) adjunctive procedure because: (I) as a sole modality, it is assumed effective only in a minority of cases [66]; (II) proximal occlusion of feeding arteries appears to be associated with recurrence [66]; and (III) it appears to increase hemorrhagic risk compared with conservative management, especially in unruptured AVMs [67].

Currently, the two most common embolization agents in cerebral AVM treatment are *N*-butyl cyanoacrylate (NBCA) and ethyl-vinyl alcohol copolymer (EVOH)-DMSO solvent (Onyx) [68, 69]. These materials are delivered in liquid form and are, hence, injectable through very narrow diameter microcatheters.

4.1 Cyanoacrylates

Cyanoacrylates solidify by polymerization initiated once they contact an anionic environment such as blood [69]. The process is very rapid but can be delayed by dilution using Lipiodol (Ethiodol in the USA) vehicle retardant. The more Lipiodol the mixture contains, the longer the delay. Optimizing dilution is a very empirical process that greatly depends on operator experience level. Cyanoacrylates' main advantages are that they: facilitate nearly instant occlusion; induce an inflammatory response within the embolized vessel walls that are believed to play an important role in the occlusion durability; are compatible in case of vascular rupture; are injectable via many microcatheter types (even the thinnest and most flexible ones currently available); have a non-glued microcatheter withdrawal that gives rise to minimal vascular network traction, so they are highly compatible with narrow diameter arterial vessels (very sensitive to traction-induced mechanical trauma); and facilitate surgical resection by helping to identify embolized vessels (compressible and easily cut with micro-scissors). Cyanoacrylates' main drawbacks are: catheter can become entrapped in the occluded vessel; difficulty in controlling the occlusion position; highly local occlusion; they can only be used by operators with extensive training; must be opacified to monitor flow during injection; and catheter position must be abandoned.

4.2 EVOH copolymer-DMSO solvent (Onyx)

Here, small polymer particles are suspended in solution using a DMSO solvent [69, 70]. Following mixture injection, DMSO diffuses to surrounding tissue, resulting in particle aggregation occluding the lumen. Flow is omnidirectional and typically includes artery reflux along the microcatheter tip. Following injections progressively colonize adjacent arteries, only then traveling towards the draining veins. Consequently, microcatheter tip trapping is a typical feature. This led manufacturers to develop catheters with detachable tips. Onyx's main advantages are: relatively high complete obliteration rate with the evidence of stability over time [70]; slow solidification facilitates prolonged/controlled injection with deeper nidus penetration; and mid-procedure angiography and reduced catheter adherence even during reflux. Onyx's main drawbacks are: DMSO is toxic—rapid injection can

cause vasospasm, necrosis, and acute respiratory distress syndrome (ARDS) [71]; DMSO-compatible catheters and syringes must be used; high radiopacity causes poor visualization during reflux in very small vessels and masking by previously embolized regions potentially leading to subsequent healthy vasculature embolization; over-reflux can potentially harm adjacent functional healthy arteries; and mixture must be shaken for at least 20 min prior to usage in order to homogenize the tantalum powder used for opacity.

4.3 Precipitating hydrophobic injectable liquid

PHIL is a recent liquid agent composed of a non-adhesive copolymer (polylactide-co-glycolide and polyhydroxyethylmethacrylate) dissolved in DMSO. Triiodophenol is used as an iodine component, being covalently bound to the copolymer for radiopacity [72]. Initial studies show embolization characteristics, embolization extent, and biocompatibility to be comparable with those of Onyx [72–74]. However, further studies are required to fully evaluate its safety and efficacy [74]. PHIL main advantages are: shorter pause times that result in significantly higher embolization success compared with Onyx; lower volumes required for the same extent of embolization compared with Onyx; it comes ready for use (does not require preliminary preparation); and improved visibility compared with Onyx. PHIL's main drawbacks are: still necessitates DMSO; embolization performance (efficacy) is only comparable with that of Onyx but does not improve on it; and could result in the exertion of traction on the vascular network upon catheter extraction.

4.4 AVM embolization complications

Post-embolization hemorrhage is the most severe, dramatic, and morbidity-mortality-related complication [75]. Up to 14% of patients exhibit neurological deficits [75, 76]. The combined death and permanent disabling neurological deficit rate is below 3.9% per patient [77, 78]. Risk predictors for endovascular treatment differ from those for AVM surgery [76]. Some studies report no morphological AVM characteristics test predict treatment complications [76]. Others suggest AVM location in an eloquent brain part, and fistula presence and a venous glue deposition are associated with complications [77]. Yet, others consider that basal ganglia location is weakly associated with new post-embolization neurologic deficits [78]. This topic is controversial. It appears that extensive devascularization and the absence of post-procedure hypotension increase hemorrhage risk [75]. Thus, partial (25–30%) devascularization per session and post-procedure hypotension induction were recommended [75]. Overall, there is a consensus that brain AVMs' embolization is associated with low overall mortality and disabling morbidity rates [77, 78]. The hemorrhage mechanisms are typically: artery perforation by a microguide/microcatheter during navigation; excessive pulling on a stuck microcatheter; and hemodynamics-related rupture due to changes in flow patterns and commination (size reduction) in venous drainage. These are typically the most severe and occur within 48 h following embolization. Finally, thrombus formation and its migration from the carrier catheter leading to ischemic complications is a feasible though non-frequent scenario.

Embolization complications dictate clear design recommendations for future endovascular devices: gradual blood vessel closure in which no abrupt flow changes take place inside the nidus; the ability to treat small and big blood vessels, easier to operate when treating patients—requiring reasonable training and experience (and skills); and avoiding exerting significant mechanical stresses on the delicate vasculature.

5. Stereotactic radiosurgery

SRS is a leading alternative to surgery or embolization, especially for AVMs located in deep or eloquent brain regions, where invasive treatment is not optional [79]. SRS employs ionizing radiation for gradually occluding AVM blood vessels. Its application was adopted from oncology during 1970–1980s [80, 81]. During the next decades, SRS (or "gamma-knife") rapidly evolved as a standalone modality and following embolization. SRS systems typically comprise a spherical array of high-focused gamma ray generators (**Figure 5**), a mechanical system that precisely positions and immobilizes patients' heads and a 3D imaging, and tracking system for treatment (i.e., dose delivery) design and real-time management (**Figure 6**). The chief benefit of radiosurgery is that it can eliminate the threat of spontaneous intracranial hemorrhage by gradual obliteration of the AVM over 2–3 years [81].

5.1 Histopathological response

Radiation induces endothelial damage (lasting biochemical changes and apoptosis), thrombocyte aggregation/development of fibrin microthrombi, and subendothelial/perivascular spindle cell proliferation (contractile myofibroblasts formed in vascular walls and AVM connective tissue—stroma) [23, 82, 83]. Both degenerative and proliferative changes are dose- and time-dependent. Degeneration expressions are tissue granulation and inflammatory cell presence in the stroma followed by type IV collagen-producing fibroblasts and fibrocytes and eventually hyaline phenotypics and obliterated vessels. Proliferation is expressed by the formation and accumulation of myofibroblasts (neointima) assumed as the canonical shrinking and occlusion factor in irradiated AVMs [23, 82, 83]. Importantly, normal vessels do not exhibit propensity to obliterate. Apparently, due to the connective tissue (stroma) surrounding the AVM nidus, pathological vessels playing a key role in the obliteration process [23, 84]. Obliteration is often followed by new vessel formation, occasionally visible on MRI [23, 82]. Radiation-induced necrosis, neural loss, myelin fragmentation, and gliosis have been detected in the surrounding brain tissue 1–10 mm from the lesion

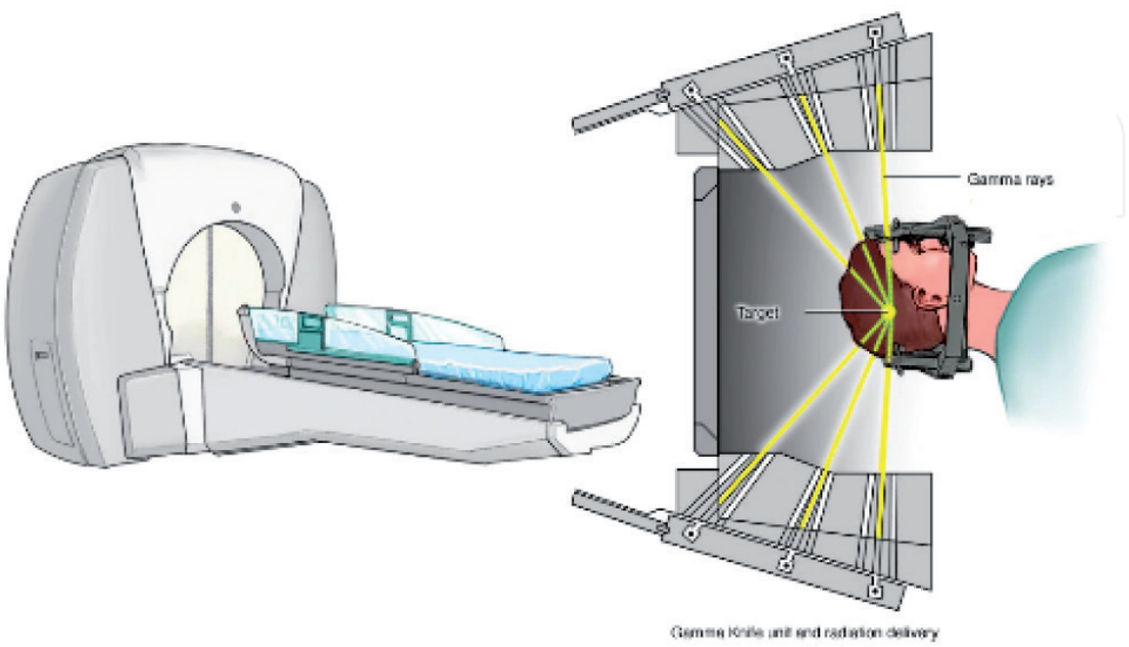

Figure 5.
Schematic illustration of a stereotactic radiosurgery procedure [© Mayo clinic].

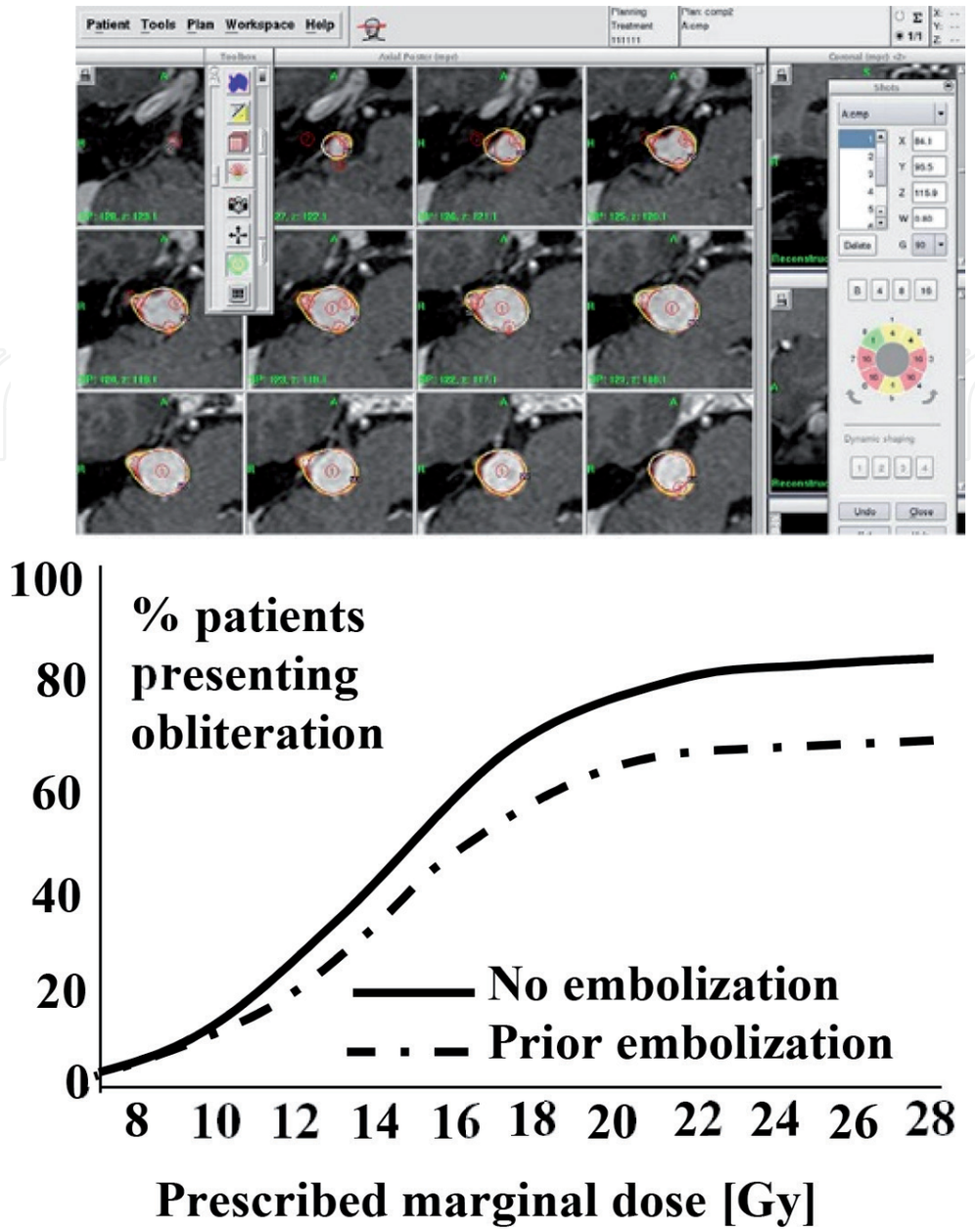

Figure 6.
Top: SRS treatment planning (dosimetry). Using imaging scans and specialized software, the treatment team determines the best combination of radiation beams to target the lesion [© Mayo clinic]. Bottom: marginal dose versus efficacy (following [81]).

border [23]. Histopathology is typically elicited and efficacy-controlled by focused irradiation of marginal doses of ~10–35 Gy (median ~20) (**Figure 6**)—delivered in a single or fractionated (higher doses) protocol [81, 82]. It has become a consensus that a better understanding of irradiation response physiology may facilitate the targeting of individual enzyme systems and open up new SRS opportunities [84].

5.2 Widely used systems

Gamma-knife systems consist of up to ~200 cobalt-60 sources arranged in circular arrays within a spherical mechanism [79]. The arrays' geometry and source strength (typically ~30 curies each) result in a 3D energy field of isodoses at any defined volume within the sphere. While each source beam dose is very low, the converged irradiation at any pre-chosen focus position adds up to clinical values. The targeted volume can be varied using different sized collimators. These systems

traditionally required complete patient immobilization—which involves direct mechanical fixation of patients' skulls using a stereotactic frame. The fixation is an invasive procedure that can be highly painful and stressful. Newer models can perform frameless treatment (thermoplastic mask for immobilization and advanced imaging for stereotactic orientation), thus supporting a less invasive patient experience. **Gantry and robotic arms systems** employ gantry-mounted linear accelerators ("LINACS") to generate the energy beam and rely on either fixed circular or multi-leaf collimators (MLCs) for its shaping. This allows a conformal scheme—which aids in treating irregular nidus geometries. Alternatively, the system can be mounted on a robotic platform (arm vs. gantry) that adds mechanical degrees of freedom. Patient positioning can also be achieved using imaging (cone beam CT) or laser systems, so frame-based immobilization systems are becoming obsolete. Less common are **proton beam systems** that accelerate protons (using a synchrotron or cyclotron) in order to generate the therapeutic beam. An advantage of proton treatment is the minimal target-exiting dose safeguarding the lesion surrounding tissue. The proton beam is typically delivered to the target volume via a gantry mechanism. Patient immobilization can be achieved invasively and non-invasively. Proton systems' main disadvantage is that they are scarce and expensive.

5.3 Treatment selection

Since radiosurgery/therapy equipment is scarce and extremely expensive, many centers and physicians have adopted particular patient selection and treatment protocols. The availability of different systems per hospital/clinic has further contributed to this diversity. The result has been that there are many controversies regarding patient and modality selection in general, and with respect to radiosurgery/therapy in particular [85]. During the last two decades, this trend has been changing as more physicians and researchers are attempting to standardize score-based radiotherapy grading and patient selection systems (see Section 4.3) [59]. A treatment selection scheme established at Pittsburgh University is presented in **Figure 7** [81]. Selection relies on AVM volume and location as well as the existence of post-treatment (residual) lesions.

Unlike SM grading in surgery, to date, there has been no distinct established treatment selection criterion for radiosurgery/therapy. Even recent advanced grading systems are not widely considered a sufficiently standardized basis for designating a patient for radiation modality. Common factors are bleeding history, patient age, existing comorbidities, anatomical location, and clinical history [81].

5.4 Outcomes and complications

Standard protocol for AVM obliteration typically involves clinical diagnostics and a half-yearly MRI, followed by annual MRI imaging. Final validation (classically at 3 years) is DSA-based, as the latter constitutes the gold standard [81]. A meta-analysis, performed by Badra et al. in 2018 [79], found that: obliteration rates are ~70–80% at 2–4 years post-treatment; annual bleeding rates are 1.1–8%; AREs are 12–38%; and overall morbidity is 4–12%. Another study showed [81]: the obliteration rates of 78% at 3-year follow-up, repeated radiosurgery needed in 12.5% of cases, post-surgery annual bleeding rates in 4.1% of cases, and AREs in 16.3%. Thus, while radiation treatment is relatively effective, it is not risk- and complication-free. Several categories merit particular attention: **acute complications** are typically related to the post-procedural presentation of neurological deficits after 2 years or more. Yen et al. studied 1426 Gamma Knife Surgeries (GKS) and found radiation-induced imaging changes (RICs, visualized as increased T2 signal surrounding the

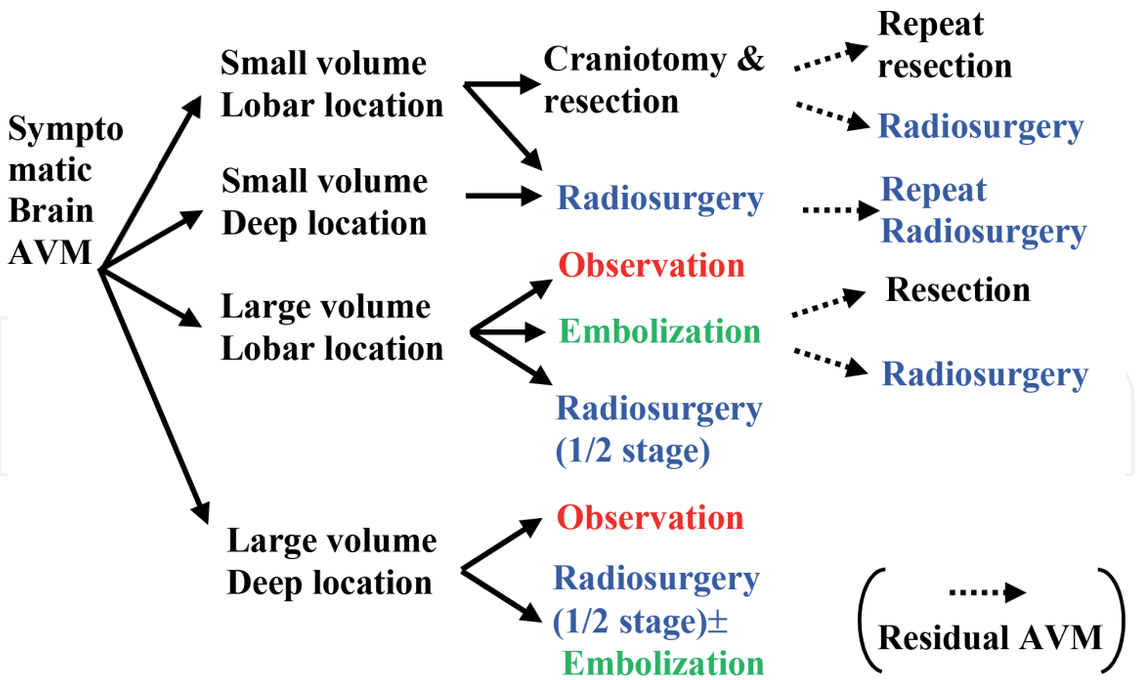

Figure 7.
AVM treatment selection scheme (following [81]).

treated nidi on MRI) that are the most common adverse effects following GKS—in 33.8% of lesions [86]. Patients with a relatively healthy brain and large nidi or with a single draining vein were more susceptible to RICs. Few RICs were symptomatic (8.6%), and most symptoms were reversible (only 1.8% had permanent deficit). About 7.7% of RICs were acute—causing a midline shift of the brain. **Late AREs** typically occur many years following SRS (6.9% of patients after a median of 8.7 years. The 5-, 10-, and 15-year incidence is 0.4, 7.7, and 12.5%, respectively). They are characterized by perilesional edema or cyst formation and are distinct from short-term (1–2 years post-surgery) AREs, often labeled as RICs [87]. About 3.4% of Late AREs are symptomatic at detection. Many that are asymptomatic later present with cyst progression. The overall symptomatic rate of late AREs is 4.7% [87]. Another study included radiation necrosis and cystic vessel formations in late ARE diagnosis and found the incidence at 2–6% [79]. Finally, since radiotherapy for AVM is based on ionizing radiation, the concern for carcinogenicity arises. However, little evidence has been found to support **radiation induced tumors** (RITs). A late retrospective analysis performed by Pollock et al. found no RITs in 471 patients observed between 1990 and 2009 (with very few others out of the total 1837 patients presenting malignant transformation) [88]. The authors concluded that the risk of RITs or malignant transformation after SRS is very low and should not be used as a justification for choosing alternative treatments. Lunsford et al. corroborate these findings [81].

5.5 Fractionated radiation/treatment

FR strategy is intended for treating large lesions that carry increased mortality and morbidity using interventional methods and lower obliteration rates or longer obliteration time when treated using radiotherapy. Unfortunately, large AVM is not a well-defined or accepted criterion in the literature. SM refer to >6 cm along the nidus largest diameter. Other studies define a volumetric condition >10 (cm^3) [62]. However, there is a consensus that high single-fraction doses as used in small AVMs increase radiation injury risks and associated neurological deficits when

large normal brain volume is exposed to high doses [89]. Two approaches exist to improve safety and efficacy in these cases: (1) **fractionation radiosurgery (FR)** where total dose is equally divided into fractions delivered over multiple sessions (days scale), so brain tissue adjacent to the lesion can tolerate higher integral doses. (2) **Volume staged radiosurgery** where the AVM is typically divided into 2–4 spatial regions each treated separately using a high single-fraction dose. Between treatments, a rest period (3–9 months) is imposed. Here, each AVM part is instantly treated with a clinically effective dose. Normal brain tissue recovers between treatments. This makes it possible to tackle the main disadvantage of FR—low fractional doses are relatively less effective at treating AVM and result in reduced obliteration rates unless the total dose is substantially increased [89]. However, a main concern of this approach is that partial AVM obliteration apparently alters blood flow patterns and increases hemorrhage risks [89]. Currently, there is a little evidence for the superiority of one approach over the other [89]. In general, it is highly recommended to minimize the integral dose to the normal brain of asymptomatic patients. Recently, Unkelbach et al. elegantly demonstrated that by boosting complementary parts of the target volume in different fractions, it may be possible to achieve a therapeutic advantage in FR since this approach facilitates mean dose reduction in the normal brain [89]. To date, FR has not been widely accepted as presenting a compelling advantage over multi-modality treatments such as initial size reduction using embolization.

5.6 Summary

While gaining popularity and presenting impressive treatment success rates of ~80%, radiosurgery still has distinct limitations that must be faced. Obliteration typically takes 2–3 years during which patients remain exposed to significant annual bleeding risks of 4–5% (twice that of conventional treatment) and overall morbidity rates reaching 12%. Large (SM grade ≥ 3) AVMs necessitate multi-modality or fractionated treatment. The latter shows promise but requires further study if efficient management is desired.

6. Surgical resection

6.1 Patient selection and outcome predictors

The SM grading system for predicting patient outcome is microsurgery-based and remains the gold standard in the field [36]. Though the physiological origins of each AVM's clinical presentation are unknown, SM and supplemental grading systems have been validated on numerous occasions (see above). These systems apply to both patient selection and outcome prediction. Recently, Kim et al. demonstrated, in a cohort study performed on 1009 AVM patients at four institutions, that supplemented SM grades (SM-Supp, also considering the patient age, bleeding history, and compact anatomy indication) have greater predictive accuracy than standalone SM grades [90]. Their findings are not unique in that they show improvement over SM. They also rightfully conclude that "current grading systems are imperfect and evolving and that as the pathophysiology, hemodynamics, and genetics of AVMs are elucidated through research, grading systems will incorporate these advances." We, however, believe that there is a great difference between academic and clinical settings. We acknowledge that complex grading schemes may present improved predictability and selection capability. However, we believe practitioners must be provided with simple, intuitive, and relatively easy-to-use schemes. Only

such schemes will be readily accepted and rapidly/easily implemented in clinical settings, particularly in emergency cases. We, therefore, recommend that the factors incorporated into future grading schemes remain relatively accessible (direct) and limited in number.

6.2 Standard microsurgery protocol

We briefly (and humbly) review key steps involved with AVM microsurgery [23, 37]. Once a patient is designated for microsurgery, **treatment planning and evaluation** begins. Often, additional imaging is performed to provide maximal data for a solid operating plan. Here, 3D reconstruction can prove very helpful and emphasis should be given to study the AVM main feeders. **Pre-operative steps** include patient positioning (one that provides a good venous return and preferably has the AVM surface aspect horizontal at the top of the approach and the longest axis of the nidus vertical) and craniotomy (removal of part of the skull to expose the brain), which provides exposure to the lesion area. Here, caution must be exerted to ensure the craniotomy is larger than the AVM surface while safeguarding the delicate dilated and exposed draining veins during dura opening (against adhesion). Only then can **AVM resection** be performed. The procedure in general is directed from the arterial towards the venous side of the nidus. All vessels must be coagulated or clipped. It is customary to leave true feeders to the end since their earlier occlusion can lead to the recruitment of blood flow from deep feeders and may cause their rupture [23]. It is important to ensure that draining veins present no evident flow. Eventually, the nidus is gently rolled out of the resection cavity**.** **Post-operative management** includes admitting the patient (while completely sedated) to the Intensive Care Unit for close observation for evidence of post-operative bleeding or swelling. A post-operative CT is typically performed shortly after the procedure to rule out any such complication followed by a mandatory angiography performed on day 2–3 after surgery.

6.3 Results and complications

The main advantage of AVM microsurgery is its "straightforward" approach, which allows relatively definite lesion resection and rapid clear follow-up. Microsurgery is considered the gold standard in AVM obliteration. It presents a high success (cure) rate reaching 99% in small SM 1–2 grades [91–93]. Treatment challenges include limitations regarding accessibility (deep locations) and a high risk of severe complications that contribute to the mortality and permanent morbidity rates of 3.3 and 8.6%, respectively, as seen in a meta-analysis performed in 2425 patients between 1990 and 2000 [8]. A more recent study found permanent mortality and morbidity rates of 1.7 and 4.8% (2.2% permanent significant morbidity) [91], and yet, another study found the permanent mortality and morbidity rates of 7.9 and 14.8% (though obliteration rate was 87.2%) [92]. Additional studies present early and permanent disabling deficits in 12.3 and 4.5%, respectively, permanent neurological deficit in 16.1% [93], perioperative neurological deficits of 17%, annual hemorrhage rate of 0.3%, and a recurrence rate of 0.9% in children [94]. These findings and others clearly demonstrate the pronounced variations in the modality outcomes depending on surgeons' expertise, patients' AVM grading distribution (e.g., 7% neurological deficits at SM Grade 1 compared with 50% at SM 5 in [90]), prior bleeding presentations, multi-modality protocol (e.g., surgery following embolization or radiosurgery as in [95]), and so forth. A review of the literature indicates that the leading risks of surgical resection are intraoperative rupture, post-operative hemorrhage, and post-operative edema. These hemodynamic events can become life threatening and disabling. Additional

complications of reduced risk are neurologic deficits from over-dissection or ischemia, seizures, hydrocephalus, and infections [23, 37]. The subject of lesion recurrence following microsurgery has been controversial. Different centers report highly varied outcomes. Recently, Aboukaïs et al. analyzed the subject and reported the recurrence as a fairly rare case (7/138 cases) affecting mostly pediatric patients. They recommend particularly long-term angiographic follow-up in children to detect AVM recurrence or remnants [96].

6.4 Emerging trends

Brain microsurgery is a proliferating field presenting many interesting developments in imaging, treatment management, surgical approach, and so forth. We very briefly mention a few promising directions. **Molecular imaging** employs specific antibodies combined with detectable agents such as gadolinium [55]. This technique was used to image particular receptors on tumors and could non-invasively detect biological markers in AVM vessels. If an appropriate biomarker imaging probe for AVM is discovered, it will facilitate highly selective lesion diagnosis and analysis. Specific conditional biomarkers (activated by physiological occupancy of enzymes, ions, and metabolites) can possibly even support super-selective procedures. Rad et al. demonstrated that vessels within the mature rat AVM exhibit elevated phosphatidylserine (PS) externalization compared with normal vessels [97]. Ionizing radiation increased PS externalization in a time-dependent manner. They concluded that the AVM localization of PS externalization may function as a tool in future SRS treatment. **Image guidance** provides a promising technique, particularly when incorporated into patient intraoperative 3D viewing and simulating systems [98]. It facilitates improved AVM localization, clearer venous anatomy, better definition of craniotomy, and so forth for the surgeons, and may reduce intraoperative risks. Spetzler and Sanai used **dynamic retraction** (retractorless surgery) and a variety of advanced handheld instruments with considerable success and suggest that fixed retraction can be supplanted by this approach, thus limiting the risk of retractor-induced tissue edema and injury [99]. There are additional promising directions outside the scope of this chapter. However, most of those mentioned (as well as those not discussed here) still lack a large enough database for establishing clinical superiority.

6.5 Summary

The neurosurgical aspect of AVM treatment presents a versatile picture. While SM Grade 1–2 lesions are treated with good efficacy and low risks (as well as a few Grade 3 cases), successful outcome rapidly declines in medium-to-large lesions, demonstrating high risk for adverse outcomes (transient and permanent neurological deficits as well as mortality). These high risks do not markedly decline when addressing large AVMs using a multi-modality approach. Perhaps because such procedures are not yet sufficiently established, we cannot currently provide this statement with distinct supporting evidence. Small AVMs constitute a large portion (~40% or so based on our literature observations) of all lesions. This leaves many cases without direct surgical solutions and greatly limits the use of this approach as a single modality. Future developments include further advancements in imaging methods, augmented reality and simulation systems, and innovative tools and approach methods. These will certainly facilitate continuous improvement in efficacy and safety with regard to small lesions and an increased ability to effectively treat medium lesions. However, we fear that treating the majority of medium-to-large lesions will continue to necessitate multi-modal, fractionated, or novel approaches.

7. Discussion and recommendations

The ARUBA trial, published in 2014, compared interventional therapy with medical management of unruptured brain AVMs. It was a broad trial involving 39 active clinical sites in nine countries. The study recruited 223 patients during the period from April 2007 to April 2013. About 114 of the patients were assigned to interventional therapy and 109 to medical management. The conclusions were that the risk of death or stroke is significantly lower in the medical management group than in the interventional therapy group (hazard ratio 0.27). Naturally, the study elicited a plethora of reactions that we will not fully cover since they are outside the scope of this review. Some, that were relatively more supportive, identified ARUBA as the only randomized trial at that time (2010) with clear clinical outcomes comparing different interventional treatments for brain AVMs with conservative medical therapy [100]. More reactions were less supportive, criticizing the pragmatic design, the patients' heterogeneity, the lack of standardization of the treatment arm, the choice of outcome measures, the short follow-up period, the small population, and so forth [87, 101, 102]. The controversy also led the European societies dealing with the treatment of AVMs to conduct a consensus conference at the European level [104]. Among the statements made were two key points which we quote: "There are sufficient indications to treat unruptured AVMs Grade 1–2 SM" and "There **may** be indications for treating patients with higher SM grades, based on a case-to-case consensus decision of the experienced team." One clear consensus emerges—further research is advocated to delineate the optimal management of unruptured AVMs, particularly those with SM grade≥3 [103]. Furthermore, judicious observation of the literature since ARUBA indicates that there may be a lacuna or at least weakness in interventional modalities when addressing high SM grade AVMs. This fact has not traversed the community unnoticed. All three main interventional modalities present a similar line—advancement in existing treatment paradigms, treatment planning, and intra-operative measures. However, to date, the core challenge persists. We feel that one possible cause is the limitations inherent in present approaches that lead to diminishing returns with every new improvement (necessitating ever-increasing technological and financial investments). The two leading avenues of interventional choice for medium-to-large lesions are currently multi-modal and staged treatment. When considering multi-modal treatment, we must take into account other factors besides medical outcomes. Multi-disciplinary AVM treatment suffers from a fundamental market/commercial flaw. Every manufacturer focuses on its core technologies (whether they are embolic agents, radiation therapy equipment, etc.), and these typically do not complement one another. This considerably impedes R&D of novel multi-modal techniques and protocols by leaving them in the hands of mostly research endeavors that lack the financial resources of commercial companies. Interestingly, this fact is clearly reflected in the literature. The number of papers we reviewed dealing with single modality treatment is an order of magnitude larger (speaking cautiously…) than those adopting a multi-modal approach. This trend continues for the number of patients treated. To conclude, we fear that multi-modal treatment faces inherent financial and technical limitations that strongly impede its chances of reaching full potential and will continue to do so in the near future. Fractionated radiation and multi-session (staged) embolization also suffer similar logistic and economic flaws. It is very challenging to repeatedly admit patients to very complex and expensive procedures also requiring highly experienced medical experts who are typically in "short supply," and advanced facilities, particularly in radiation treatment. Considering this state of affairs, we conclude that it could be advantageous to consider a treatment approach that has not been used to address AVM in the past—continuous mild

irradiation provided via an implantable active source. The use of such implants in Brachytherapy is very well established and dates back decades (if not a century). Much knowledge has been accumulated in the field (we will not review the subject due to lack of space). Such an implant has the potential to elicit a hyperproliferative effect facilitating lumen closure by thickening of the vascular wall by exploiting the "candy wrapper" or edge effect (see further data below).

First, let us attempt to convince the readers that this approach merits medical investigation. In Section 6.1, we explained that there are two major changes in tissue when exposed to radiation—degeneration and proliferation. Both changes are dose- and time-dependent. Therefore, there is room for adjusting and augmenting each by controlling radiation kinetics and spatial distribution patterns. Active stent studies show proliferation and restenosis reduction (typically in-stent) but also induction (typically at the stent edges). Albiero et al. implanted 122 32P radioactive β-emitting stents (activity levels of 0.75–12.0 μCi) in 91 lesions in 82 patients [105]. After 6-month follow-up, they found that intrastent restenosis was 0–16% (depending on implant activity; high activity stents showed no restenosis). However, they also found that restenosis at stent edges was 41–52% (maximal for the lowest activity stents!). They concluded that the use of active stents in patients with coronary artery disease is feasible and named this edge effect as the "candy wrapper." They speculated that the effect was a result of low radiation at the stent edges combined with an aggressive approach to stenting (pre-dilatation with an oversized balloon). Shortly after, they also demonstrated that stents with higher initial activity levels of 12–21 μCi (54 lesions) reduced intrastent neointimal hyperplasia compared with stents of 3–12 μCi (42 lesions) [106]. However, they did not eliminate edge restenosis (38% for the lower activity stents were reduced just to 30% for the higher activity stents). Since they used a non-aggressive stent implantation strategy (pre-dilatation with a non-oversized balloon) in the second study, they also ruled out that the edge effect is attributable to the implantation procedure. Wardeh et al. implanted 31 stents in 26 patients [107]. They corroborated this deduction (also attributing the edge effect to low radiation levels) and concluded that the use of low activity radioactive stents is safe and feasible. Sianos et al. analyzed 175 human vessels (131 were eventually eligible) treated according to the beta-radiation in Europe (BRIE) study protocol [108]. They wanted to evaluate the impact of Geographical Miss (GM—a situation in which the radiation source does not fully cover the injured vessel segment) on edge restenosis after intracoronary beta-radiation therapy. The injured edges of the effective irradiated segment (EIRS) constituted the GM edges. Restenosis was defined as diameter stenosis >50% at follow-up (6 months). They found GM affected 41.2% of the edges and significantly increased edge restenosis to 16.3% compared with 4.3% in non-GM edges (for both proximal and distal edges). GM associated with stent injury increased edge restenosis more than that associated with balloon injury (from 3.6% with no GM to 18.75% compared with from 5.36 to 10.71%, respectively). However, EIRS restenosis was similar between vessels with and without GM (24.3 and 21.6%, respectively), thus indicating a dominant effect for radiation fall origins. Van der Giessen et al. investigated the edge effect in the coronary arteries of Yucatan micropigs [109]. They fabricated half radioactive and half non-radioactive stents (n = 20, with 10 regular stent controls). Their design introduced a mid-stent radioactive dose falloff zone next to a non-radioactive stent-artery transition at one side and a radioactive stent-artery transition at the other side. They demonstrated a significant mid-stent stenosis at 4 weeks follow-up. Two animals died suddenly because of coronary occlusion at this mid-zone at 8 and 10 weeks. At 12 weeks, there was a significant neointimal thickening at the mid-stent dose-falloff zone of the half-radioactive stents but not at the stent-to-artery transitions at both extremities. No mid-stent response was observed in the

non-radioactive stents. They concluded that the edge effect is associated with the combination of stent injury and radioactive dose falloff. Studies performed on both human subjects and animal models found a significant neointimal increase at low activity stents edges [110]. These findings seem clinically significant since low-dose-related neointimal hyperproliferation, when compared with conventional radiosurgery, does not appear to be associated with damage to the Tunica Adventitia or Vasa Vasorum, hyaline phenotypes, or any endothelial disfunction (degeneration traits). Desouky et al. recently reviewed the targeted and non-targeted effects of ionizing radiation [111]. They describe cell and tissue response to low-dose/dose rate ionizing radiation. Cells exposed to such radiation exhibit increased cellular communication and resistance to future irradiation. They conclude that exposure of human cells to low radiation induces molecular processes that are different from those induced by high dose radiation. Furthermore, the effects of ionizing radiation are not restricted to irradiated cells but also affect non-irradiated cells via mechanisms termed "Radiation Bystander Effects" and "Radioadaptive Response" [111]. This suggests that a low-dose/dose rate source can potentially affect a larger volume than that anticipated from direct energy absorbance evaluations based on our experience with high-energy treatments.

The edge effect has always been treated as an adverse phenomenon. However, in AVM treatment, the objective is precisely the opposite of most traditional vascular procedures—obliteration rather than revascularization. Here, we suggest that if exploited properly, this effect may prove highly beneficial. Let us explain its potential advantages:

- An implant can be introduced in a minimally invasive manner by an interventional neuroradiologist alongside embolization or standalone. The expertise required for these procedures overlaps considerably.

- Gradual closure of the blood vessels will not elicit rapid hemodynamic irregularities that are well known to induce adverse effects such as hemorrhage.

- A single implantation procedure yields short overall operative/hospitalization time with FT or staged embolization. No recurrent patient admittance also ensures adequate costs compared with staged interventional procedures (also considering hospitalization charges).

- The literature indicates that lumen occlusion in these settings requires months. This can possibly lead to a shorter overall treatment period compared with FT or staged embolization (that can take up to years) and thus reduce hemorrhage risks.

- Treatment time for SRS is typically up to ~2 h. For FT, let us multiply it by up to 5 which is a common session number—indicating ~10 h. Let us now assume that the continuous source is decaying over a period of just 3 months ~3*30 day/month*24 h/day = 2160 h. This indicates that a dose rate more than a 1000 times smaller compared with that which is used in SRS or more than 200 times smaller compared with FT could eventually provide the same overall absorbed energy. This is clearly not a sufficient medical proof since we know FT is less efficient than radiosurgery in obliteration rates and we certainly have no evidence of the effectiveness of such a source type and radiation levels in the AVM context. However, it does clearly indicate the potential for dose-rate reduction. Many AREs that originally motivated FT could be inherently circumvented when mild constant radiation is employed instead of short-lived

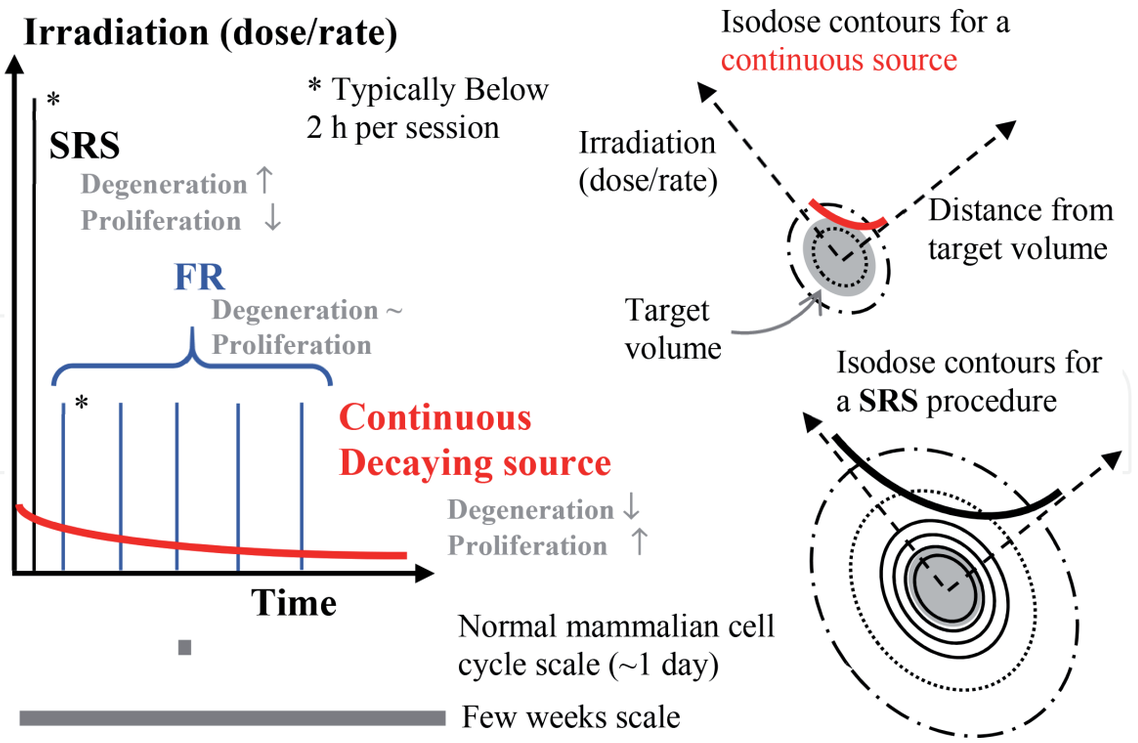

Figure 8.
Illustration of the conceptual differences between the presumed radiation traits required from a continuous source and those required from the current two predominant treatment modalities—radiosurgery and FT. Left: radiation dose/rate kinetics. Right: isodose map (the same dashing indicates equal radiation levels). The continuous source is constantly effective, thus necessitating significantly reduced doses/rates and facilitating a much better contained radiation distribution field, reduced affected brain volume, and potentially reduced AREs.

high-intensity energy doses/rates. Mild radiation also ensures a much better contained isodose distribution compared with the target volume and thus affected brain volume (**Figure 8**).

- A mammalian cell cycle typically lasts around a day (~24 h). A treatment lasting up to 2 h will not overlap with each of the cell cycle stages. However, a continuous source will expose the lesion cells to radiation during each of their cell cycle stages. We know from cancer treatment experience that this can prove highly beneficial. No data is available to indicate this also applies in the case of AVM treatment. However, this is certainly a point to consider.

- There is a mature and experienced medical device/implant industry that can reasonably rapidly adjust to develop and fine-tune such implants to AVM clinical requirements.

- Device/implant procedures are relatively easily attuned to qualify for reimbursement regulations, so insurance companies and medical centers can adopt the treatment modality.

- In contrast with embolic agents, a radiation source does not have to occupy each and every AVM blood vessel because it inherently supports a collateral effect. This leaves a very wide and flexible working range for the physicians regarding the final implantation position.

To conclude, if proven feasible, low-radiation implants could add several unique benefits to AVM treatment and we advocate studying their use.

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