

Section 1

Biology

Chapter

Pathology of cavernous malformations

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Cerebrovascular malformations are classified as cavernous malformations (CMs), arteriovenous malformations (AVMs), developmental venous anomalies (DVAs) and capillary telangiectasias (CTs). CMs are the second most common form of cerebrovascular malformation and constitute up to 10–15% of the total [1,2]. In the past, CMs were not visualized on radiological examinations such as CT scanning or angiography and were therefore referred to as angiographically occult or cryptic vascular malformations. Recent studies have resurrected the old suspicion that CMs are vascular tumors [3], hence the alternative terms cavernous hemangiomas, cavernomas, or cavernous angiomas. Clinical features of CMs include epilepsy (22–50%), focal deficits (20–45%), headaches (6–34%), or hemorrhages (up to 56%); CMs may also remain clinically silent (up to 40%) [4–8].

Macroscopic and microscopic features

CMs resemble well circumscribed, multilobulated, mulberry-like structures ranging in size from a few millimeters to several centimeters in diameter [2,9,10]. Intracranial CMs are more frequently located supratentorially (64–84%) while spinal lesions are frequently located in the lower thoracolumbar region (97%) [2,11,12]. They have been observed in all cortical locations as well as in deep locations like the basal ganglia, thalamus, cerebellum and the brainstem [2,13,14]. Lesions of the cerebellopontine angle, pituitary, and periventricular region have all been reported to have intraventricular CMs [15–17].

The histological features of CMs are best understood in the context of normal vascular anatomy. Normal cerebral blood vessels are lined by endothelial cells joined by tight junctions. The endothelial layer is

surrounded by a basal lamina. While capillaries have just the endothelial cell layer, all other vessels have one or more layers of smooth muscle cells as well as some pericytes immediately adjacent to the endothelial cells. Surrounding the entire vessel are astrocytic endfeet which comprise the glia limitans. Together, the endothelial cells, their tight junctions, and the astrocytic endfeet form the morphologic basis of the blood–brain barrier.

Like capillaries, the blood vessels of CMs lack smooth muscle cells and have a homogeneous, hyalinized appearance in sections stained with hematoxylin and eosin (Fig. 1A). The overall arrangement of vessels is compact, with the classic appearance being one of back-to-back vessels without intervening parenchyma. However, most lesions also contain some areas with more loosely packed vessels [18]. Thrombosis is common in these low-flow malformations as well as acute, organized, and recanalized thrombi, or even completely occluded vessels (Fig. 1B). Calcification is common both within vessel walls and within the adjacent parenchyma. In our unpublished series of 24 patients who underwent surgery for CMs, 58% had thrombosis, 41% had calcification, and 4% (one case) showed intervening parenchyma; the true incidence of these processes was likely higher, as the volume of material sampled was small.

CMs are generally surrounded by a rim of fibrosis with associated hemosiderin deposition (Fig. 1C). The appearance of this tissue is distinctive enough to be strongly suggestive of cavernous angioma in the proper setting [19]. Hemosiderin may also be present in the adjacent neuropil, where it may be responsible for occurrence of seizures [20]. In our series, 92% of CMs showed hemosiderin, with reactive astrocytosis in 29%.

Section 1: Biology

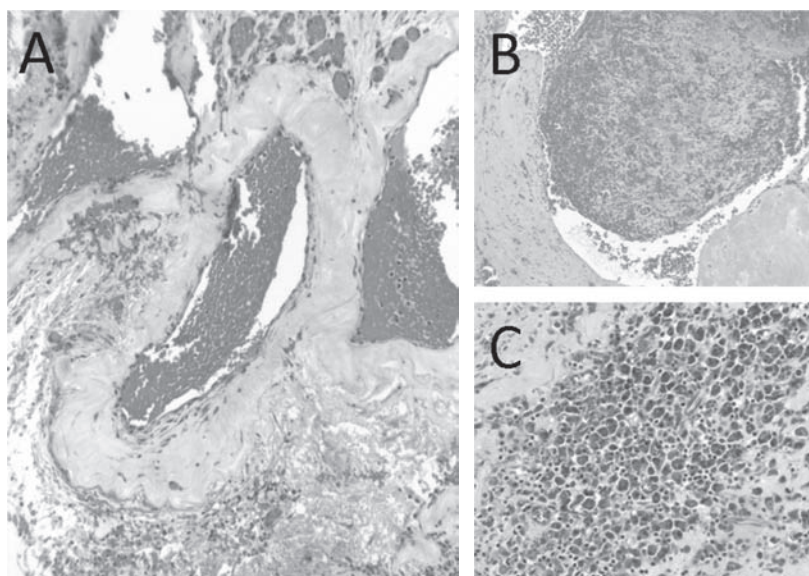


Figure 1.1. (A) The back-to-back blood vessels of cavernous malformations have thick, amorphous walls. (B) The blood vessel shown here contains a recent thrombus. (C) Densely packed hemosiderin-laden macrophages are often found within or around the rim of a cavernous angioma. See color plate section.

Immunohistochemistry of cavernous malformations

The vessels of CMs have also been studied using immunohistochemistry. Endothelial cells, astrocytes, and extracellular matrix proteins have all been studied. Expression of angiogenic growth factors, proliferation markers, and molecules associated with angiogenesis has also been examined.

Many of the common endothelial cell markers are proteins that are potentially important in endothelial cell interactions with platelets or with the coagulation system. One of the endothelial cell markers that are most commonly used for identification of endothelial cells is CD31 (platelet endothelial cell adhesion molecule PECAM 1). CD 31 is involved in endothelial migration and angiogenesis and is expressed normally in CMs by both immunohistochemical and *in situ* hybridization techniques [21]. Expression of another common marker, von Willebrand factor (a platelet-vessel wall mediator in the coagulation system), is normal [21,22], as is the expression of thrombomodulin [22]. Thus, there is no evidence from these immunohistochemical studies that endothelial cell abnormalities are responsible for the frequent thrombosis seen in CMs.

As the vessel walls within CMs contain virtually no smooth muscle cells, immunostains for smooth muscle actin- α show no reactivity within vessel

walls. However, normal endothelial cells often contain small amounts of actin and that is also the case for the endothelial cells within CMs [23]. The subendothelial layer may also contain actin immunoreactivity, likely in the basal lamina. Kilic *et al.* have suggested that the expression of smooth muscle actin- α could represent an immature molecular construction in CMs compared to AVMS [23]. Collagen IV, fibronectin, and laminin were similarly present in the endothelium and subendothelium, but not in the amorphous portion of the vessel wall. There was relatively more fibronectin staining than laminin staining, a pattern that is also seen in early stages of angiogenesis. Faint staining for collagen III was present in the subendothelium only [23].

There have been a number of studies examining markers of angiogenesis in CMs. The best studied is vascular endothelial growth factor (VEGF), which is found in the endothelium and subendothelium, though more so in adults than in children [24–26]. The VEGF receptor Flk-1 is found in endothelial cell nuclei. Basic fibroblast growth factor (bFGF) and transforming growth factor- α (TGF- α) are also found in the endothelial cells of adults and children, with no difference between the two age groups [24–26].

Hypoxia inducible factor-1 α (HIF-1 α), which is involved in oxygen homeostasis, is present in cavernous angiomas, in all layers in a pediatric study

[26] and in endothelium in an adult study [24]. Endoglin, a normal endothelial antigen, a part of the TGF-beta1 and beta3 receptor complex and the gene mutated in hereditary hemorrhagic telangiectasia Type 1, is also present in pediatric and adult samples [24,26]. Of note, it has been suggested that endoglin may be important in vascular development and in vascular remodeling in response to increased blood flow or shear stress [26,27].

Endothelial cell proliferation has been documented by positive labeling using antibodies to proliferating cell nuclear antigen (PCNA) and the Ki-67 epitope (MIB-1) [24,26].

Etiology

Cavernous malformations are generally believed to be congenital lesions presenting at any age from the neonatal period through adulthood. They may occur sporadically or with familial clustering. The familial forms of lesions have been attributed to mutations of the CCM1, CCM2 and CCM3 genes and are expressed as autosomal dominant phenotypes with penetrances of 60–88%, 100% and 63% respectively [28]. Although the role played by the products of CCM genes is yet to be established, animal models suggest that these are critical to angiogenesis and that the loss of their function leads to dilatation of major vessels, defective endothelial association and barrier function, and dysfunctional sprouting [29]. The detailed role of these genes is discussed in the chapters “Clinical and molecular genetics of cerebral cavernous malformations” and “Molecular biology of cerebral cavernous malformation”.

De novo appearance of CMs has been reported following brain irradiation [30], brain biopsy [31], and viral infection [32]. Exposure to such stimuli may initiate a reactive angiogenesis or cause mutations leading to local loss of expression of CCM genes leading to *de novo* appearance of CMs [33–35]. Some authors have associated hormonal influences with *de novo* occurrence of CM such as a case with follicle stimulating hormone producing pituitary adenoma described by Pozzati *et al.*, wherein new lesions appeared [30]. Lüdemann *et al.* also reported *de novo* appearance of CM in a pregnant patient but failed to demonstrate estrogen or progesterone receptors on immunohistochemical staining, suggesting that new lesions appear independently of hormone levels, contrary to what was widely considered [36].

CMs and other vascular malformations

Like CMs, other types of vascular malformations have characteristic macroscopic and microscopic features. Capillary telangiectasias (CTs) are composed of aggregates of thin-walled vessels indistinguishable from normal capillaries and separated by normal intervening brain parenchyma. While CMs are well circumscribed radiologically, CTs may sometimes appear as a nebulous blush [37]. Developmental venous anomalies (DVAs, sometimes termed venous malformations) are collections of abnormally dilated veins forming a caput medusa draining into a large central vein. As described below, these frequently occur with CMs in their vicinity. DVAs do not tend to bleed, and the intervening brain tissue appears normal. Arteriovenous malformations (AVMs) contain tortuous, anastomosing blood vessels. Some of the vessels resemble true arteries or veins, but most are abnormal vessels of varying diameters whose walls are formed primarily by collagen rather than by smooth muscle. Intervening parenchyma is found across the lesion but is almost absent at the densely packed nidus of the lesion. The intervening and surrounding parenchyma is often hemosiderin-stained and gliotic. Calcification is common.

Although various intracranial vascular malformations were initially described as distinct entities based on the factors described above, both MRI examinations and the histological features observed at surgery or autopsy suggest that different types of malformations may exist within the same patient. Moreover, individual lesions may have features of more than one type of malformation, suggesting intermediate forms. In the case of CMs, coexistent DVAs or CTs have been frequently reported [38–43]. Rigamonti *et al.* described the coexistence of features of typical CT as well as CM in two (10%) of 20 patients who underwent resection of CM [39]. One patient had multiple lesions including both CT and CM. Staining for smooth muscle actin revealed smooth muscle in the walls of 20% of the lesions, indicating the presence of arterial or venous differentiation. Brain parenchyma was interspersed between vessels in 35% of the patients, a feature generally attributed to CTs rather than CMs. Rigamonti *et al.* [39] and others have concluded that CM and CT constitute part of a larger spectrum of intracranial vascular malformations. For example, Awad *et al.* described two (14.2%) patients with coexisting CT and CM in a series of 14 mixed vascular

Section 1: Biology

malformations. Histopathological examination revealed zones of CTs in the surrounding brain parenchyma that eventually coalesced into the CMs [44].

Rigamonti *et al.* reported the first evidence of a high association between CM and DVA and suggested a possible pathogenetic relationship [38]. Abdulrauf *et al.* confirmed that 13 of 55 patients (24%) with CM had associated DVA [43]. Similarly, Wurm *et al.* reported 25.8% of CMs were associated with DVAs in a series of 58 patients [45]. In contrast, Porter *et al.* reported DVA associated with CMs in all of his surgically treated patients whereas preoperative MRI revealed such lesions in only 32% of 73 patients [46]. The latter result suggests that the association may be underestimated as MRI may not always detect DVAs [45,47]. Recognition of such combined pathology may be important as CMs associated with DVAs may have a greater predilection to bleed and be symptomatic than lesions which are purely CM [43]. The increased bleeding tendency of CMs associated with DVAs has been hypothesized to result from venous hypertension

[43,48]. Dillon cited stenosis at the junction of the DVA and central vein as a possible cause of elevated venous pressures in DVAs [41]. It has been suggested that hemorrhagic recurrences and organization of the resulting thrombus initiate the process of angiogenesis, which may cause growth of CMs through an ongoing process of hemorrhage and ischemia [48]. In support of this idea, others have demonstrated that DVAs are composed of mature blood vessels and are formed earlier in embryogenesis [49], while CMs are immature vascular lesions with active angiogenesis. More recently Abe *et al.* classified venous anomalies into two distinct types: venous malformations which are not DVAs that are angiographically occult and contain compact venous channels devoid of smooth muscle layers; and angiographically detectable dilated venous channels draining normal white matter and communicating with cortical veins [47]. Abe *et al.* suggested that angiographically occult venous malformations can be safely resected without significant sequelae, indicating anatomical

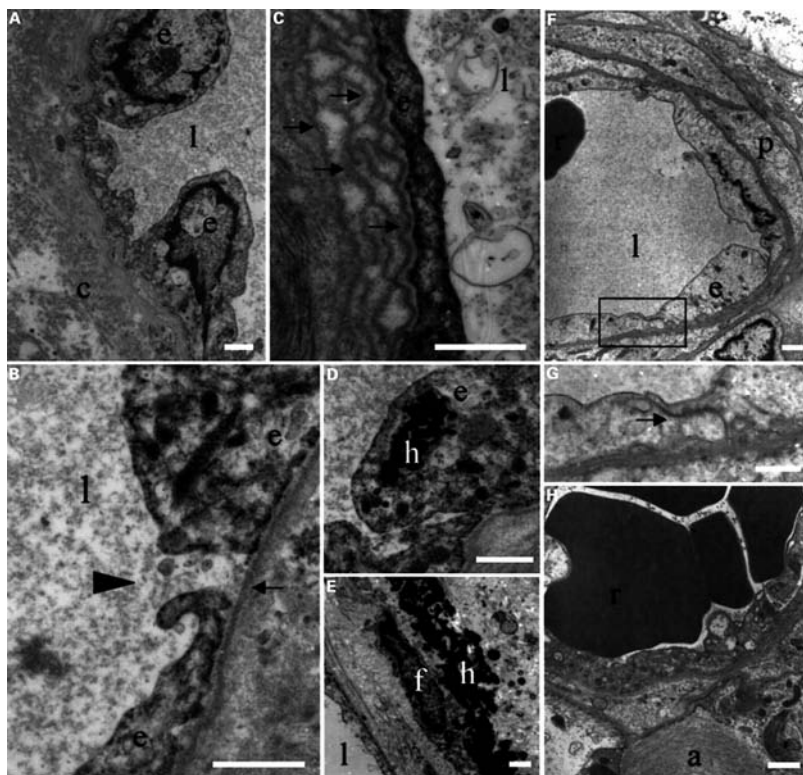


Figure 1.2. Electron micrographs of cavernous malformations (A-E) and microvessels in adjacent normal brain (F-H). (A) Ultrastructurally, these lesions consist of endothelial cells (e) lining vascular sinusoid lumens (l) and surrounded by a dense collagenous matrix (c). No perivascular cells were seen and the endothelial basal lamina was in direct contact with the collagenous matrix. (B) Gaps (arrowhead) between adjacent endothelial cells were seen in cavernous malformations where the lumen (l) was exposed directly to the basal lamina (arrow). (C) In focal areas, the basal lamina (arrows) demonstrated multiple abnormal layers. (D,E) Haemosiderin (h) could be seen within endothelial cells (D) and within microns of the lumens of the vascular sinusoids (E). A rare fibroblast profile (f) is seen in (E) in the connective tissue matrix. (F) A cerebral microvessel from brain tissue adjacent to a lesion demonstrates typical encircling pericytes (p) separating the endothelial cell basal lamina from the neuropil. A red blood cell (r) is noted in the lumen. (G) Magnification of the boxed area in F demonstrates a tight junction (arrow) between adjacent endothelial processes. (H) Another microvessel from the surrounding brain is being contacted by an astrocyte foot process (a) containing abundant intermediate filaments. Scale bar shown in all images represents 1 μm. Reproduced from [49] with permission from BMJ Publishing Group.

and pathophysiological differences from DVAs [47]. It is possible that such venous malformations may remain undetected on MRI until they are revealed on pathological examination.

Ultrastructure and pathophysiology of CMs

The ultrastructure of blood vessels within cavernous angiomas differs markedly from that of normal cerebral vessels, with abnormalities in endothelial cells that would predict an impaired blood–brain barrier, increased extravasation of red blood cells, and structural weakness.

Such changes may help explain the pathophysiology of the growth, hemorrhage, and epilepsy caused by CMs.

Like their normal counterparts, the vessels of cavernous angiomas are lined by endothelial cells, the somata of which are relatively unremarkable. However, there are associated features, which would be expected to interfere with the normal blood–brain barrier. For example, the endothelial cells have been described as having few if any tight junctions [49], with those junctions that are present being described as intermediate or poorly formed [50]. There may be gaps between endothelial cells [49–51] (Fig. 1.2). The basal lamina that underlies the endothelial cells has been reported both as present [49,50] and as thin or absent [51], perhaps depending on whether the malformation has bled [51]. Previous hemorrhage has also been associated with changes in the endothelial cells themselves, including more filopodia and increased numbers of Weibel–Palade bodies, micropinocytotic vesicles, filaments, and other organelles [51].

In the vessel walls, pericytes and subendothelial smooth muscle cells are lacking or are very poorly formed. The walls also lack organized collagen and elastic fibers, which would make them more likely to bleed [50,51]. Astrocytic endfeet are also lacking [49,51].

Summary

CMs are vascular malformations composed of endothelial lined dilated vessels (caverns) packed together without intervening neural parenchyma. CMs are both hereditary and sporadic. They can be seen with a history of previous irradiation and viral infection. The low flow rate and luminal pressures inside CMs make them angiographically occult and less likely to

bleed than other vascular malformations. However, microscopic extravasations, hemorrhages, thrombosis with areas of reorganization, calcification, and inflammation are common features. Ultrastructural studies have demonstrated a dysfunctional blood–brain barrier with poorly formed tight junctions, and the presence of Weibel bodies in lesions with recurrent bleeds. CMs and other vascular malformations are known to coexist and such lesions are more likely to bleed and recur after resection. Further research in the etiopathogenesis and genetics of CMs will help elucidate the pathobiology of CMs.

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Section 1: Biology

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Chapter 1: Pathology of cavernous malformations

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Epidemiology and natural history of cavernous malformations

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Cavernous malformations (CM) are multilobulated lesions composed of sinusoids derived from endothelium embedded in collagen matrix without histological elements found in mature vasculature [1]. CMs may be found at any location in the central nervous system and therefore can present with diverse clinical presentations like seizures (23–50%), headaches (6–52%), and focal deficits (20–45%) arising from mass effect or lesion hemorrhage; however, up to 40% of patients may be asymptomatic [2]. Most CMs are found supratentorially. They are usually characterized clinically by seizures and less commonly by inconspicuous growth or intermittent bleeding. Seizures caused by perilesional deposits of epileptogenic hemosiderin may become intractable [3]. Hemorrhages associated with CMs are of low pressure and frequently clinically asymptomatic [4]. When a lesion is present in eloquent locations like the brainstem, however, even a small bleed can cause clinically significant neurological deficits [5]. The natural history of CMs is affected by several factors like gender, lesion location, and genotype. This chapter discusses the natural history of CMs and its clinical relevance.

Etiology

Cavernous malformations may be of sporadic or familial type. Familial CMs are caused by mutations of CCM1 or CCM2 or CCM3 genes [6–9]. Most reports have described familial lesions in patients of French or Hispanic descent, but familial occurrence may be more widespread than these reports suggest [9–12]. Most CMs including sporadic lesions were historically considered congenital lesions; however, several cases of their *de novo* appearance following

brain irradiation or viral infection have been reported [13,14]. It is believed that *de novo* appearance of CMs occurs in genetically predisposed individuals [15].

Prevalence

CMs constitute 10–15% of all vascular malformations and are the second most commonly found vascular malformation after developmental venous anomalies (DVAs), which are found in about 4% of the population and represent up to 63% of all cerebrovascular malformations [16–18]. The estimated prevalence of CM by MRI-based studies has been reported to be 0.4–0.53% of the general population, while on autopsy series the prevalence of CM is about 0.4% [19–21]. Up to 20% of CMs are asymptomatic, making it more difficult to accurately study their epidemiology and natural history. CMs were frequently not detected (occult) by radiological investigations like angiography or CT scans. This has changed since the advent of MRI; now these lesions are increasingly diagnosed in the asymptomatic population [16,22]. Thus accurate understanding of their natural history has become critical to appropriate management of these patients.

Asymptomatic CMs are frequently diagnosed amongst the relatives of patients harboring familial CMs [10,12,23,24]. Rigamonti *et al.* diagnosed three (27.3%) asymptomatic individuals out of 11 relatives diagnosed with familial lesions while Zabramski *et al.* found 39% (12 individuals) prevalence of asymptomatic lesions in a population of 31 relatives of patients harboring familial lesions [12,23]. Conversely, others have suggested a prevalence of symptomatic lesions (approximately 60%) amongst patients with the familial form of cavernous malformations [25,26]. At least 6–10% of all patients harboring CMs may have a pattern of inheritance consistent with familial lesions [27,28].

Section 1: Biology

Furthermore, it is estimated that while 10–15% of Caucasian patients have familial lesions, 40% of Hispanic patients have familial CM [29]. Most existing studies describe the epidemiology of familial CMs based on screening of relatives of symptomatic patients with multiple CMs; however, the population prevalence of the sporadic type is yet to be studied.

Lesion characteristics

The typical measurements of cavernous malformations range from 0.01 to 1.7 cm [16,30,31]. Multiple CMs have been reported by several series, but are more frequently found in patients with a history suggestive of inherited CMs than in sporadic cases [2,16]. Multiple lesions are present in 50–84% of familial cases but in only 10–33% of sporadic cases [32,33,34]. *De novo* occurrence of lesions is more common in familial forms [35,36] and there exists an apparent association between the number of lesions and the age of the patient, with older patients having a greater number of lesions, suggesting *de novo* occurrence during the life of the patient [35,36].

CMs are more often supratentorial (64–84%) than infratentorial (19–35%) [16,37,39], with a distribution proportionate to the volume of neural tissue. The most common supratentorial locations are the frontal and temporal lobes while the most common infratentorial locations are the pons and the cerebellum [16,20]. CMs may rarely be found at locations like the cerebello-pontine angle, optic chiasm, pineal and pituitary gland, and third or fourth ventricles [33,40,41]. CMs may be found in association with other vascular malformations like developmental venous anomaly (DVAs) or capillary telangiectasia [16,42]. When associated with DVAs, CMs are more likely to bleed, with an incidence of 62% as compared to a 38% incidence of hemorrhage amongst CMs without a draining DVA [17]. These lesions also had a greater incidence of recurrent bleeding (23%) than when CMs were present with DVA (9.6%) [17]. This has been attributed to a higher intraluminal pressure within the lesion associated with DVA [43,44].

Natural history of cavernous malformations

Although the natural history of cavernous malformations has been investigated for more than 50 years, it is still difficult to clearly describe it due to a lack of comparability between studies. Most studies differ in

patient characteristics (pure familial cases versus combination of familial and sporadic cases; population-based versus hospital-based series), study design (retrospective versus prospective studies) and the criteria defining hemorrhage (extra-lesional versus intra-lesional, occult versus clinically significant bleeds) [5,12,23,38,39,45–49]. Consequently, wide variation can be observed in reported rates of hemorrhage, ranging between 0.25% per person years to 4.2% per person years [20,37,45,50]. Thus, it is impossible to make a statement regarding the natural history that is consistent with all the reports in the literature. It follows that clinical decisions based on the interpretation of these studies remain challenging.

Despite disagreements on the natural history of CM and its predictors, most studies have shown a relatively benign course of superficial lesions compared to deep lesions or those located infratentorially with respect to bleeding [16,31,45]. In an MRI-based study Del Curling *et al.* reported an overall bleeding rate of 0.25% per person years of exposure [39]. Multiple lesions were present in six (18.75%) of the patients in this series; after accounting for the multiple lesions the risk of bleeding was reduced to 0.1% per lesion per person year of exposure. Similar to these findings, Robinson *et al.* described a hemorrhage rate of 0.7% per lesion per person year of exposure in a series of 66 patients with six patients (9%) presenting with a bleed at the start of the study and only one patient suffering a bleed on follow-up of 143 lesion years of observation [20]. In contrast to this, Kondziolka *et al.* reported a higher overall bleeding rate of 2.63% per person year [47]. However, due to referral bias, deep or infratentorial lesions constituted over 50% of this study population. Thirty-five percent of patients harbored brainstem lesions, of which 62.8% had a previous hemorrhage. Another 17% had thalamic or basal ganglia lesions. Overall about 50% of the study population suffered at least one previous hemorrhage from the lesion as compared to the series by DeCurling *et al.*, which included no patients with a prior history of bleeding, and patients presented with 72% of their lesions in a supratentorial location [39]. Similarly Porter *et al.* in a series of 173 patients followed for 437 person-years reported a higher bleeding or deficit rate in deep locations as compared to superficial locations (10.6%/year versus 0%/year: $p = 0.001$) [45]. MRI-documented bleeding rates were 1.6% per year for deep versus 0% per year for superficial lesions. Furthermore, the multivariate analysis in this study