CEREBRAL CAVERNOUS MALFORMATIONS
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Cerebral cavernous malformation (CCM) diagnosis occurs more frequently than some years ago, due to the increased diffusion of magnetic resonance imaging. Progress in knowledge on genetical and molecular pathogenesis may change management strategy of these patients allowing more tailored approaches. Moreover, treatment techniques and expertise are evolving too. Lesions deserving treatment, a better approach to follow-up and screening, treatment management and what could be expected from it - all these issues have a growing importance and need a multidisciplinary data sharing and discussion. Prevention of rebleeding in eloquent areas and management of drug resistant seizures in CCM patients are key targets of CCM treatment. Aim of this volume is to provide a window on several points of view from biological aspects, through diagnostic methods and treatment approaches, ranging from observation to surgery and radiosurgery. A pharmacological approach to prevent bleeding of CCM and possibly their regression is also being investigated at an experimental level. The surgical approach is particularly challenging since CCM are small lesions which require a very precise, minimally invasive and targeted approach based on the specific anatomic location, which might become especially demanding in eloquent areas or in the brainstem. Several authors shared their impressive case series with us.

This volume is addressed to experienced neurosurgeons, neurologists, neuroradiologists, geneticists, molecular biologists and all neuroscientists interested in cerebrovascular lesions.

We auspicate that the present studies can provide a starting point for further developments and interesting discussions and perhaps encourage collaboration among referral centers for CCM, also involving other researchers and colleagues who can help CCM patients.

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Cerebral cavernous malformations (CCM) are enlarged vascular lesions consisting of closely clustered, abnormally dilated and leaky capillary caverns that affect up to 0.5% of the general population. CCM can manifest as a broad range of symptoms typically in the 2nd to 5th decade of life, including cerebral hemorrhage, seizures, chronic headaches and neurological deficits, among others. However, around 50 - 80% of CCM cases are asymptomatic, and CCM lesions are often discovered incidentally on magnetic resonance imaging (MRI). Symptomatic, hemorrhagic lesions are generally treated surgically, although lesions located in the brainstem are particularly challenging and associated with high surgical morbidity. Currently, there is no approved medical therapy available for treating CCM.

Both sporadic and familial forms of CCM exist. Sporadic cases of CCM are characterized by a lack of family history of the disease and usually the presence of a single lesion on MRI, although multiple lesions have been observed. In contrast, familial cases mostly exhibit multiple lesions that show progression in both number and size over time. Familial CCM follows an autosomal-dominant inheritance pattern with incomplete penetrance, and has been linked to heterozygous loss-of-function mutations in three different CCM genes: CCM1/KRIT1, CCM2/MGC4607, and CCM3/PDCD10. However, 5-15% of familial cases cannot be explained by the three known CCM genes, suggesting the existence of additional CCM loci. CCM lesion genesis is thought to follow a “two-hit” mechanism, requiring biallelic germline and somatic mutations in one of the three known CCM genes. Somatic mutations in CCM genes were identified in the endothelial cells of CCM lesion tissue, highlighting the importance of endothelial cells as the primary site of CCM lesion pathogenesis.

A spectrum of mutation types have been identified within the three known CCM genes, allowing for better characterization of phenotype-genotype correlations. The wide variability in phenotypes seen among carriers of the same gene mutation also suggests the influence of additional genetic and/or environmental modifiers. Patients with mutations in different CCM genes may follow a different clinical course, but genetic testing is often not undertaken for patients with multiple CCMs in clinical practice. In this review, we update and discuss the importance of screening the three CCM genes using different methods to identify mutations predisposing to CCM. We also highlight the main clinical symptoms according to CCM gene mutation status and additional clinical features associated with CCM. Finally, we discuss...
future prospects for elucidating the molecular basis of CCM as well as genetic modi-
 bers of CCM disease severity and progression. Understanding the genetic archite-
 ture of CCM is essential for an earlier diagnosis of the disease, predictive testing of at-risk patients, and design of appropriate medical therapies of which there are currently none available.

From discovery of CCM loci to recent progress
in defining the molecular basis of CCM

Sporadic and familial CCM cases: genetic mutations in CCM-1, -2 or -3

Identification of CCM loci

In 1995, the first CCM locus (CCM1) was identified on chromosome 7q by several
groups studying large Hispanic and non-Hispanic families with multiple affected
relatives.24-26 Johnson et al. refined the 7q region of interest from approximately 40-
cM to 4-cM, containing four potential candidate genes.27 Shared haplotypes were
detected between affected members in three Hispanic CCM families, suggesting a
common ancestral mutation.27 Hispanic-American familial and sporadic CCM cases
demonstrated inheritance of the same haplotype from a common ancestor by high-
density microsatellite genotyping within 7q.28 In non-Hispanic CCM families, some
studies confirmed the linkage to 7q,25, 29, 30 while others excluded this region, sug-
gesting the presence of additional CCM loci.31 In 1998, Craig et al. investigated link-
age in twenty non-Hispanic Caucasian CCM families and reported two novel loci:
CCM2 at 7p and CCM3 at 3q.32 Additional studies replicated linkage to the CCM2
or CCM3 locus and also indicated genetic heterogeneity among non-Hispanic CCM
families.33, 34

Identification of CCM genes and mutations

In 1999, the CCM1 gene or KRIT1 (Krev Interaction Trapped 1) on chromosome
7q was discovered using a genomic sequence-based positional cloning strategy.10
Seven different CCM1/KRIT1 mutations were reported in 23 distinct CCM families,
including the “common Hispanic mutation” (CHM-Q455X, rs267607203), which
explains the majority of CCM cases occurring in Hispanic-American families of
Mexican descent.10 In 2001, computational and experimental analyses detected
four additional coding exons in CCM1/KRIT1, resulting in corrected annotation
of the CCM1 genomic sequence, and the discovery of another novel frameshift
mutation.35

In 2003, Liquori et al. selected eight candidate genes out of 55 identified at the 7p
CCM2 locus, on the basis of biological relevance.11 Sequence analysis identified eight
different mutations in nine CCM families in the CCM2/MGC4607 candidate gene,
encoding malcavernin protein.11 Denier et al. also identified MGC4607 as the CCM2
gene and reported 2 large deletions as well as eight point mutations in CCM2 in 30
families with CCM.12 In 2005, Bergametti et al. identified the CCM3 gene or PDCD10
(programmed cell death 10) on chromosome 3q, using high-density microsatellite
genotyping in 20 CCM families.13 A de novo deletion within PDCD10 was identified
as well as six deleterious mutations in non-Hispanic Caucasian CCM families.13 Fig-
Figure 3.1.—Chronological discovery of CCM molecular basis.

Figure 3.1 shows the chronological milestones in the discovery of the molecular basis of CCM.

Overall, the majority of CCM patients have mutations in *CCM1*. Sequencing of coding exons and intron-exon junctions in genomic DNA of all three *CCM* genes has identified a mutation in 95% of familial cases and 57% of sporadic cases with multiple lesions. In a screening study of 163 consecutive CCM patients, mutations were identified in 128 (78%), including 53% in *CCM1/KRIT1*, 15% in *CCM2/MGC4607*, and 10% in *CCM3/PDCD10*. Among 122 CCM patients with identified mutations, 65% were in *CCM1*, 19% in *CCM2*, and 16% in *CCM3*. Among sporadic CCM cases from two Italian studies, germline mutations were identified in 1.3% to 5.5% in *CCM1*, 2.5% to 2.6% in *CCM2*, and 0% in *CCM3*. Studies in French, Swiss and German cohorts have reported similar findings. Thus, a minority of sporadic cases is due to germline mutations in *CCM* genes, which could be inherited or de novo.

Not all disease-causing mutations are small coding changes detectable by sequencing. Other methods such as multiplex ligation-dependent probe amplification (MLPA), quantitative multiplex PCR of short fluorescent fragment (QMPSF) or array-based comparative genomic hybridization (array CGH) are required to detect larger insertions/deletions, duplications and other copy number and structural changes associated with CCM. MLPA studies in *CCM1-3* mutation-negative probands have detected large genomic deletions or duplications within all three *CCM* genes, indicating that large genomic rearrangements represent a major component of CCM disease. For example, a common 78-kb deletion spanning exons 2-10 of *CCM2* has been found in 13% of CCM families screened in a US study, while a larger screening study estimated that 18% of all mutations in *CCM1, CCM2*, or *CCM3* are due to large deletions. Such large rearrangements can also encompass additional flanking genes, which could contribute to the disease phenotype, such as in a rare syndromic case featuring both CCM and Greig cephalopolysyndactyly syndrome due to a large deletion on 7p14-13 encompassing both *CCM2* and *GLI3*. In addition, cDNA sequencing may be necessary to characterize candidate intronic variants resulting in a splicing defect, and can also reveal CCM mutations resulting from other types of genomic rearrangements. For example, an intronic *CCM1* insertion causing extension of transcription into an intron and
resulting in a premature stop codon was detected in a CCM family with multiple affected individuals who had CCM lesions on MRI but were asymptomatic.\textsuperscript{3} Such findings expand the \textit{CCM} mutation spectrum and highlight the importance of screening the three \textit{CCM} genes using different methods to identify mutations.\textsuperscript{3,14}

The Angioma Alliance, a patient advocacy group for those affected with CCM, maintains a database of reported CCM mutations (www.angioma.org/mutation).

\textbf{CCM pathogenesis: a two-hit mechanism}

Until the early 2000s, the pathogenic mechanisms underlying CCM lesion genesis remained unknown. The presence of multiple lesions in familial and single lesions in sporadic CCM cases inspired the hypothesis that somatic mutations may contribute to CCM lesion genesis according to a “two-hit” mechanism, resulting in biallelic inactivation of one of the \textit{CCM} genes in lesion cells. In 2002, Kehrer-Sawatzki \textit{et al.} investigated for the first time DNA isolated from CCM tissue and identified two \textit{CCM1/KRIT1} somatic mutations in a CCM lesion from a sporadic case.\textsuperscript{45} Following these findings, several studies attempted to validate this “two-hit” mechanism hypothesis with varying success, likely due to limited sensitivity of genetic screening methods used at the time.\textsuperscript{15,46-48} In 2005, Gault \textit{et al.} reported a familial CCM case with a germline \textit{CCM1-CHM} mutation that also harbored a somatic \textit{CCM1} deletion in surgically-resected CCM lesional tissue.\textsuperscript{15} These findings strongly supported the “two-hit” hypothesis in CCM lesion genesis and were replicated in other studies, showing biallelic germline and somatic mutations in \textit{CCM1}, and also in \textit{CCM2} or \textit{CCM3} in familial cases.\textsuperscript{15, 18} Akers \textit{et al.} also found that these somatic mutations occurred in endothelial cells from CCM tissue by laser capture microdissection, highlighting endothelial cells as the primary site of CCM lesion pathogenesis.\textsuperscript{16, 18} Even with highly sensitive next generation sequencing technology, somatic mutations were detected only in a fraction of endothelial cell DNA from CCM tissue, pointing out the heterogenous nature of the lesion. Recently, McDonald \textit{et al.} confirmed that sporadic cases of CCM can also follow this “two-hit” mechanism, reporting the presence of one or two biallelic somatic mutations in CCM lesions from sporadic cases.\textsuperscript{17}

Mouse models of CCM also support the “two-hit” hypothesis, as heterozygous \textit{Ccm1} or \textit{Ccm2} mutant mice do not spontaneously develop CCM lesions.\textsuperscript{47, 49} Indeed, \textit{Ccm1} heterozygous mice need to be crossed into a mismatch repair-deficient \textit{Msh2}\textsuperscript{-/-} or \textit{Trp53}\textsuperscript{-/-} background, increasing the rate of somatic mutations, to exhibit CCM lesions.\textsuperscript{47,49} However, \textit{Ccm2}\textsuperscript{-/-}/\textit{Msh2}\textsuperscript{-/-} mice did not manifest CCM lesions in contrast to \textit{Ccm2}\textsuperscript{-/-}/\textit{Trp53}\textsuperscript{-/-} mice, showing the complexity of modelling human inherited diseases such as CCM in mouse models.\textsuperscript{49,50} Recently, Shenkar \textit{et al.} reported that \textit{Ccm3} heterozygous mice exhibit CCM lesions without \textit{Trp53}\textsuperscript{-/-} or \textit{Msh2}\textsuperscript{-/-} background,\textsuperscript{51} suggesting other pathogenetic mechanisms underlying CCM lesion genesis and echoing phenotypic differences in severity between CCM1/2 and CCM3 disease discussed below.

\textbf{Genotype-phenotype correlations: wide variability among CCM patients}

\textit{Sporadic vs. familial CCM cases}

Sporadic cases of CCM are characterized by a lack of family history of the disease and usually the presence of a single lesion on MRI\textsuperscript{5, 6} although multiple lesions have been observed.\textsuperscript{7, 8} In contrast, familial cases mostly exhibit multiple lesions that can
appear de novo and increase in size over time. Other imaging phenotypes have been reported to differ between sporadic and familial CCM cases. Petersen et al. reported a higher incidence of developmental venous anomaly associated with a CCM lesion in sporadic (44%) compared to familial CCM1-CMH cases (1.2%). More recently, patients with familial CCM1-CHM were reported to have a higher prevalence of white matter abnormalities (15.4%) in comparison to age-matched cohorts of sporadic CCM (2.5%) and healthy controls (2.1%); adjustment for vascular risk factors did not explain the increased frequency of white matter abnormalities among familial cases. The reasons explaining these differences between sporadic and familial CCM cases are unknown, however they suggest the possibility of a different developmental mechanism underlying CCM pathogenesis for sporadic and familial cases.

**CCM1 and CCM2 mutation carriers**

Over the last decade, studies have started to describe phenotypic differences by CCM gene mutation status. Most of these studies initially focused on CCM cases due to mutations in CCM1 and CCM2, as those genes were discovered first and are the most common causes of familial CCM.

In 2004, Denier et al. evaluated for the first time genotype-phenotype correlations in a large Caucasian cohort of 202 familial CCM subjects harboring CCM1/KRIT1 mutations. Most CCM1 mutation carriers were symptomatic (62.4%), presenting initially with seizures (in 55% of cases) and cerebral hemorrhages (32%), followed by focal neurologic deficits (9%) and headaches (4%); the mean age of clinical onset was 29.7 years. The number of CCM lesions was highly variable: 84.6% of subjects had two or more lesions on MRI, 26 subjects (12.9%) harbored only one lesion, and five subjects (2.5%) had no lesions. In 2006, the identification of the third CCM gene enabled evaluation of genotype-phenotype correlations between CCM1, CCM2 and CCM3 mutation carriers. The number of symptomatic subjects was lower in the CCM2 group (55.2%) in comparison to CCM1 (63.4%) and CCM3 (67.9%) groups; however, the initial clinical symptoms were similar among the three groups. Further, CCM2 mutation carriers had a lower number of gradient-echo sequence lesions in comparison to CCM1 or CCM3 mutation carriers, and the number of lesions increased more quickly with age in CCM1 than in CCM2. These results suggested overall that CCM2 mutation carriers may have a milder phenotype than CCM1 and CCM3 mutation carriers.

In addition to the main clinical symptoms related to the cerebral lesions, other clinical features can occur in CCM patients. In 1999, hyperkeratotic cutaneous capillary venous malformation (HCCVM), a distinctive cutaneous vascular malformation composed of abnormal capillaries and venous-like vessels, was described in 4 French CCM families. Genetic linkage analysis mapped HCCVM to the CCM1 locus on chromosome 7q, suggesting that both HCCVM and CCM were due to the same genetic abnormality. The mutation causing CCM and HCCVM was discovered in exon1 of KRIT1 causing an early premature stop codon; downstream mutations in KRIT1 only seemed to be linked to the CCM phenotype in these families, suggesting a possible molecular-phenotypic correlation. Others have also reported cutaneous vascular malformations in CCM1 mutation carriers, including café-au-lait skin lesions, capillary malformations, venous malformations, or cavernous hemangiomas. Interestingly, HCCVM has only been reported in CCM1 patients, suggesting that HCCVM may be a specific clinical feature of CCM1 disease. Thus, in a subset of CCM1 families, there is an additional risk of approximately 40% for coexisting cutaneous...
vascular lesions, some of which are cosmetic but others may cause functional problems. Retinal cavernomas have also been associated with CCM, and found in approximately 5% of familial CCM cases with mutations in any of the three CCM genes. Familial CCM cases carrying a CCM1 mutation can also present with multiple vertebral and/or spinal cavernous angiomas. Spinal cavernous angioma has also been reported in a CCM2 mutation carrier. Further, hepatic angiomas have been observed in CCM1 patients. The presence of angiomas in the brain, spinal cord, skin, retina, vertebral column, and liver suggests CCM vascular involvement in numerous tissues both within and outside the central nervous system (CNS). The extra-CNS involvement may pose additional risks to CCM patients, and also serve as a marker for possible CNS involvement in otherwise asymptomatic cases.

**Recent insights: CCM3, the most severe form of CCM disease**

Until recently, little was known regarding the phenotypes of CCM associated with CCM3 mutations, as the CCM3/PDCD10 gene was the last gene to be discovered and the number of CCM3 mutation carriers was limited. Recent case series have described a number of clinical features specific to CCM3 patients. Riant et al. reported that around 90% of CCM3 patients presented with multiple CCM lesions and, as previously suggested, cerebral hemorrhage was the initial manifestation in patients under 20 years of age. A second study also suggested that children with CCM3 mutations had significantly more CCM lesions in comparison to children with CCM1 mutations. Other studies supported the early-onset of clinical features in CCM3 patients, and a higher risk of early-onset cerebral hemorrhage in comparison to CCM1 and CCM2 patients. Shenkar et al. also reported that CCM3 patients had a higher risk of recurrent bleeding after a first hemorrhage. Additional clinical features related to CCM3 were also described, including presence of skin lesions as previously described, severe scoliosis that can lead to spinal fusion, cognitive disability, and presence of multiple meningiomas or other brain tumors. While skin lesions have also been reported in CCM1 and CCM2 patients, these other features appear specific to CCM3 patients. Thus, CCM3, although more rare than CCM1 and CCM2, appears to be associated with more specific and severe phenotypes of CCM disease, as well as an earlier age of onset.

**Future prospects**

**Other CCM genes?**

As discussed above, approximately 20% of familial or sporadic cases with multiple CCMs screened have no genetic mutation identified. Some of the cases in which a mutation is not found are likely due to technological issues and mutation type, but others probably represent further genetic heterogeneity of the disease and suggest the possibility of other CCM loci. Ethnic differences have been reported in CCM genetics, supporting this hypothesis and providing an avenue toward identification of new CCM genes. Recently, a study in Japanese CCM cases with multiple lesions found that CCM2 mutations seem to be more prevalent than CCM1 or CCM3 mutations, compared to Caucasian CCM cases. In this study, mutations in CCM1, CCM2 and CCM3 accounted for 12.5%, 37.5% and 12.5% of the sporadic multiple CCM cases,
respectively, in comparison to 20%, 30% and 10% of the familial cases. Thus, nearly 40% of Japanese CCM cases screened lacked a mutation within the three known CCM genes, which is twice the frequency in Caucasian CCM patients.

Overall, the fact that: 1) a fraction of familial CCM remain genetically unexplained; and 2) the fraction explained by mutations in CCM-1, -2 and -3 genes may differ by ethnicity, indicates that other CCM genes remain to be discovered. For example, Gianfrancesco et al. reported a case of a 30-year-old female patient that exhibited CCM lesions and premature ovarian failure with a balanced translocation involving chromosomes 3 and X. Any causative mutation or genomic rearrangements in the CCM1, CCM2 and CCM3 genes were excluded for this patient, suggesting that a different gene was responsible for CCM. Characterization of this translocation by fluorescence in situ hybridization revealed an interruption of ZPLD1 (zona pellucida-like domain containing 1), and expression levels of ZPLD1 were reduced 2.5-fold in lymphoblastoid cells from the CCM patient as compared to those in healthy controls. However, no mutation was detected in ZPLD1 when screening CCM-affected families negative for CCM1, CCM2 and CCM3 mutations, suggesting that CCM due to ZPLD1 mutations might be relatively uncommon, or that disruption of the function of a different gene than ZPLD1 underlies the CCM phenotype in this patient. Further studies are needed to establish the function of the ZPLD1 gene and confirm its possible role in CCM pathogenesis. With the recent advent of high-throughput exome and genome sequencing for the discovery of genes underlying rare Mendelian disorders, we anticipate that the discovery of novel CCM genes will provide future directions for CCM research.

**Genetic modifiers in CCM disease severity and progression**

There is a wide variability in phenotypes among CCM patients, even among those with the same CCM gene mutation. The reasons for this variability are unknown, but likely include other genetic, environmental or lifestyle factors. Balasubramanian et al. described two CCM families presenting with highly variable manifestations of a CCM1/KRIT1 mutation, ranging from tonic-clonic seizures at 18-months of age to asymptomatic. We recently reported an association of cardiovascular risk factors, such as obesity and systolic blood pressure, with the number of CCM brain lesions in a cohort of 185 familial Hispanic patients, all harboring the CCM1-CHM mutation. In our cohort of CCM1-CHM mutation carriers, 63.2% of subjects were symptomatic at presentation with intracerebral hemorrhage as the main clinical symptom leading to CCM diagnosis; lesion burden ranged from 0 to 713 on susceptibility-weighted MRI. Interestingly, a rare case of CCM monozygotic twins harboring a CCM1/KRIT1 mutation allowed comparison of disease manifestation and clinical course in the presence of an identical genetic background. The initial manifestation was seizures at the age of 19 years for both twin sisters, and each had an identical number of two CCM brain lesions. However, the localization of CCM lesions and clinical course were different, probably due to the random nature of somatic mutations. In contrast to the wider intrafamilial variability usually observed between siblings, these findings show greater similarity of disease onset in monozygotic twins, suggesting the influence of additional genetic modifiers in non-twin siblings. In CCM3 disease, a three generation family segregating a CCM3 mutation was reported, showing a wide spectrum of clinical manifestations, including acute childhood cerebral hemorrhage in the proband, skin lesions in the mother, and multiple meningiomas in the maternal grandfather.
Additional genetic variation either within the CCM1/2/3 genes or in CCM signaling pathway genes may explain phenotypic differences between CCM1/2/3 mutation carriers. A large Italian family, consisting of 15 CCM subjects harboring a KRIT1/CCM1 deletion and 8 subjects without the causative mutation, was screened for additional genetic variation within CCM1, CCM2 and CCM3 genes. Numerous genetic variations were identified in the three CCM genes, which may modify expression or function of the CCM1/CCM2/CCM3 protein complex, thus explaining the observed phenotypic variability. However, additional studies in other large CCM families and functional studies are needed to draw stronger conclusions.

Recently, we investigated common genetic variation in inflammation and immune response pathways in 188 Hispanic patients harboring the CCM1-CHM mutation, as those pathways play an important role in CCM pathogenesis. We identified common variants associated with markers of CCM disease severity, including history of intracerebral hemorrhage, total number of CCM lesions, and total number of large lesions (≥5mm in diameter). In particular, rs9823731, a common intronic polymorphism in the TGF-β receptor 2 gene (TGFBR2) was associated with all three markers of CCM1 disease severity examined, supporting the involvement of TGF-β signaling in CCM disease, as previously suggested. Thus, TGFBR2 might be a key participant in the mechanism underlying CCM disease severity and phenotype variability.

Many studies have investigated the function of CCM proteins, their binding partners and the potential mechanisms through which these proteins may act within blood vessels to lead to CCM lesion formation, as extensively reviewed elsewhere. These recent advances in CCM protein signaling suggest new candidate modifiers of CCM disease to explore. As an example, the Heart of Glass (HEG) receptor has been demonstrated to interact with CCM1, CCM2 and CCM3 proteins in a signaling pathway involved in heart and vascular development. Zheng et al. investigated the role of HEG in CCM formation by using mouse models and human studies of patients with familial CCM. The study revealed HEG as one of the upstream activators of CCM signaling but did not find a role for HEG in the postnatal pathway underlying CCM pathogenesis. These findings suggest that other modulators of CCM signaling and CCM pathogenesis remain to be discovered.

Conclusions

Over the last decade, significant progress has been made in defining the molecular basis of CCM and identifying disease mutations within the CCM1/KRIT1, CCM2/MGC4607 and CCM3/PDCD10 genes. Recent studies have indicated the importance of systematically including different mutation screening methods to increase the chance of identifying insertions, deletions and other large genomic rearrangements and provide a comprehensive CCM genetic diagnosis. It is now apparent that CCM3 cases can present earlier and with a more severe phenotype than CCM1 and CCM2 cases, but more clinical studies in larger cohorts of well-phenotyped sporadic and familial CCM cases are needed to further investigate genotype-phenotype correlations. Moreover, it is of particular interest to examine other environmental and genetic modifiers in CCM disease severity and progression, which may explain the significant phenotypic heterogeneity of the disease and provide insight into the natural history and pathophysiology of CCM. Knowing
the specific genetic mechanisms underlying different forms of CCM disease, gene targets, and whether phenotypes differ by gene mutation will be important for targeted design of specific medical therapies to help slow or prevent CCM lesion formation and progression.

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20. Balasubramanian M, Jain V, Glover RC, Robertson LK, Mordekar SR. Cerebral cavernous malformation:


Earlier and more reliable radiological detection due to the wide availability of magnetic resonance imaging (MRI), as well as our better understanding of their natural history, has significantly changed management strategy of cerebral cavernomas (CCMs, also known as “cavernous malformations”, “cavernous angiomas”, or “cavernous hemangiomas”) during the last decade.\(^1\) However, due to their heterogeneity and the lack of high quality evidence, their optimal management is still debated.\(^2\) Consensus seems to exist in the treatment of hemispheric (superficial) CCMs: observation for incidental and microsurgery for symptomatic lesions in eligible patients. However, there is a degree of equipoise for deep and eloquent lesions in the brainstem, thalamus and basal ganglia, especially for those after one or no hemorrhage, because they seem to behave more aggressively if untreated, while any intervention would carry a higher risk.\(^3\)

Stereotactic radiosurgery (SRS) was introduced for the treatment of CCMs based on the assumption that their pathological vessels would respond similarly to arteriovenous malformations (AVMs), which are known to undergo thrombo-obliteration after SRS.\(^4\) However, neither MRI nor catheter angiography can demonstrate their cure after SRS.\(^5\) Moreover, early attempts of SRS often resulted in high rate of complications.\(^5\)\(^-\)\(^8\) Thus, the questionable outcome of SRS and recent improvement in microsurgical techniques led to skepticism dominated amongst neurovascular experts 10-15 years ago regarding SRS.\(^9\) During the last decade, however, increasing numbers of publications reporting good clinical outcome after treatment with modern radiosurgical technique from all over the world appear to support the initial intuition.\(^5\) SRS is generally recommended as a treatment option for surgically inaccessible CCMs with repeated hemorrhages, but some large centers have recently recommended SRS early soon after the first presentation.\(^10, 11\) The rationale behind this policy is to avoid the stepwise neurological deterioration caused by repeated hemorrhages of deep-seated lesions. In order to widely adopt this proactive policy we need to answer the two major critical questions raised by still existing opponents.\(^12, 13\) Should SRS be considered a real alternative for microsurgery for symptomatic cases in terms of efficacy, and alternative for wait-and-see policy in a neurologically intact patient owing to its safety? Due to the heterogeneous quality of evidence regarding natural history,\(^2\) management\(^14, 15\) and specifically published data on CCM SRS\(^5, 16, 17\) it is not easy to dispel concerns. In this paper we review the current literature of CCM SRS and critically analyze published data.
based on our recently suggested standard criteria, specifically addressing the issues frequently raised by critics while arguing for the safety and effectiveness of modern CCM SRS.

Natural history of cavernomas

The key in management strategy and for proper interpretation of results of SRS is the understanding of natural history of CCMs. Although this Journal will provide details, let us consider a few main figures. These lesions, with an estimated prevalence of 0.15–0.9% and distinct pathological and MRI characteristics (Figure 9.1), compose a large proportion of the previously described angiographically occult vascular malformations (AOVM). Seventy-six percent of CCMs are located supratentorially, 8% in the basal ganglia/thalamus, and 18% in the brainstem. Approximately 19% of the patients harbor multiple lesions, more frequently in familiar forms comprising at least 6% of all cases. Of the 6 cases detected per million per year, 47–60% were asymptomatic at detection. Only 9.3% of the lesions initially found incidentally or presented with seizures go on to cause hemorrhage or focal neurological deficit within 5 years, but the risk of a second event increases to 42.4%. When patients become symptomatic, typically in their 30s, 37% present with seizures, 36% with hemorrhage, 23% with headaches, and 22% with focal neurological deficits.

Hemorrhage from cavernomas

The aim of CCM treatment is either to control seizures caused by the lesion or to prevent hemorrhages and consequential neurological deterioration. The definition of clinical hemorrhage is far from obvious. Not all clinical events (acute neurological deterioration) are associated with evidence of concurrent hemorrhage, while hemosiderin ring is almost always present even in asymptomatic cases. The latter is

Figure 9.1.—A| T1-; B| T2-weighted; C| and gradient echo axial MR images of a patient with multiple CCMs. The left occipital symptomatic lesion with evidence of subacute and chronic hematoma has a type I appearance and was surgically removed. A type III incidental lesion is found lateral to the wall of right occipital horn (asterisk) and three type IV incidental lesions in the right frontal lobe are best visible in gradient echo image (arrows).
explained by ultrastructural studies that suggest a compromised blood-brain barrier at the site of a CCM that may lead to a chronic erythrocyte leak into the surrounding brain and to consequential deposition of hemosiderin even in the absence of clinically significant hemorrhage.\textsuperscript{31, 32} We recommend to adapt the definition of clinical hemorrhage described by Al-Shahi Salman \textit{et al.}\textsuperscript{24} it is a clinical event with acute or subacute onset symptoms with radiological, pathological, surgical, or cerebrospinal fluid evidence of recent extra- or intralesional hemorrhage, whereas the mere existence of a hemosiderin ring or the sole increase in diameter are not considered as hemorrhage.

Despite evidence of de novo CCM formation,\textsuperscript{23, 33} retrospective studies assuming lesion presence since birth gave similar estimates for first ever hemorrhage rates as prospective studies, 0.1-2.7%/lesion/year \textsuperscript{18, 19, 51-56} or 0.25-3.1%/person/year.\textsuperscript{18, 30, 34-36} A first bleed may destabilize a CCM and increase the risk of further bleeding, which is supported by the majority of observational studies with only few exceptions.\textsuperscript{36, 39} Prospective studies estimated the rebleed rates between 4.5 and 33.77%/year,\textsuperscript{38, 40} and the cumulative incidence of rebleed was found 56% after 5 and 72% after 10 years.\textsuperscript{41} Several studies suggest that increased rebleed risk is time limited and decreases few years after the first hemorrhage ("temporal clustering").\textsuperscript{37, 41, 42} However, this is not a universal finding \textsuperscript{43} and even if this were the case, the risk for rebleed seems to be increased for at least 5 years after initial bleed.\textsuperscript{44, 45} Brainstem and thalamic/basal ganglia CCMs are generally observed to have higher initial and rebleed rates (2.3-8.7 and 12.4-60%, respectively).\textsuperscript{34, 46, 47} One recent observational study on pediatric patients with brainstem CCM demonstrated that the hemorrhage-free survival was only 13.7% at 15 years.\textsuperscript{48} It is not clear, however, whether deep-seated CCMs are more prone to bleeding, or whether any bleed is more likely to be symptomatic due to higher functional density of deep eloquent structures.

Deep eloquent CCMs also have a higher risk of persisting morbidity caused by a single hemorrhage. Morbidity of superficial hemispheric CCMs after a bleed usually manifests in epilepsy and only rarely in focal neurological deficit,\textsuperscript{49, 50} while a single bleed from a deep eloquent CCM leads to persisting neurological deficit in up to 40-60% with a substantial risk of mortality.\textsuperscript{34, 43, 45, 51, 52} Moreover, the chance for permanent disability cumulatively increases with each subsequent bleeding episodes.\textsuperscript{45, 53} and only 19% of pediatric patients harboring hemorrhagic brainstem CCM recovered fully at 4 years.\textsuperscript{48} It is, therefore, fundamental for informed therapeutic decision-making to consider the difference between first and repeated hemorrhages and also the distinct behavior of superficial and deep-seated lesions. It is also possible, that there are even more distinct subpopulations, some lesions behaving aggressively with a high risk of rebleeding (temporarily or for a much longer period after a first hemorrhage), whilst others are more quiescent. This is supported by immunohistochemical studies demonstrating proliferation of abnormal endothelial cells in CCMs with recurrent bleeds.\textsuperscript{32} Lesions with the complete absence of tight junction immunoreactivity have also been found to have significantly higher propensity to develop major hemorrhages and perilesional edema.\textsuperscript{54} However, the proportion of these more unstable lesions is unknown and currently we are unable to predict from clinical or radiological signs which pattern of behavior a CCM would follow, but can only rely on lesion location and prior hemorrhage in our clinical judgment.
Radiosurgery of cavernomas

Rationale for cavernoma radiosurgery

It is well documented that radiation induces hyalinization and thickening of the wall of the endothelium-lined pathological vessels of AVMs leading to progressive thrombo-obliteration. The idea to use SRS for AOVMs was initially based on the assumption that the majority of these lesions were partially thrombosed AVMs and therefore the vessels would be further obliterated by high dose focused radiation, as observed in the pathological vessels of true AVMs. Although later histopathological studies found most AOVMs to be CCMs, early clinical studies demonstrated that these lesions had responded in a similar timescale to true AVMs, with reduction of rebleed rate within a 2-year latency period after treatment. Moreover, histological studies of surgically resected previously irradiated CCMs showed to some degree similar radiation-induced vasculopathy as seen in AVMs: fibrinoid necrosis, endothelial destruction, hyalinization, marked fibrosis and scar tissue formation. Although complete obliteration was also found with signs of neovascularisation, a comparative study reported only about 20% luminal reduction in CCMs after SRS. Of note, these specimens came from lesions that remained symptomatic after irradiation, and those rendered silent by the treatment may actually show complete response, were they removed for analysis. Alternatively, hyalinized vessel walls (“scaring”) of such a low pressure lesion may sufficiently stabilize it to prevent a rebleed even without full obliteration.

The effect of cavernoma radiosurgery on epilepsy

SRS may be a real treatment alternative for microsurgical resection in patients with intractable epilepsy in several conditions, such as eloquent location, the patient’s medical condition, or the patient’s preference. A retrospective multicenter study demonstrated that 53% of the patients suffering from long lasting epilepsy refractory to medical therapy became seizure free (“modified” Engel Class IA and B), 20% showed significant (Class II), and only 26% little or no improvement (Class III and IV) within a mean of 4 months after SRS. Patients with CCM located in the mesial temporal lobe had worse outcome. More recent studies found similar results, 39-54% of the patients became seizure free (Class I), and 14-20.5% improved significantly (Class II). A meta-analysis found that 31% of the patients became seizure free (Class I) and 35% improved significantly after SRS. On the first look this seems inferior to surgical series, as Class I response was achieved in 69% of the surgical cases refractory to previous medical therapy. However, considering pre-intervention seizure duration SRS appears to be as effective as surgery if applied early after seizure onset. While 90% of the patients treated with SRS improved with short history of epilepsy (≤3 years) and only 38.5% with longer lasting epileptic disease, 81% improved with ≤1-year history and 70% with longer duration of epilepsy in the surgical group. Moreover, good outcome could only be achieved microsurgically with complete removal of both CCM and the surrounding hemosiderin ring even in the short history group (90.5% versus 60% with partial removal).

The effect of radiosurgery on hemorrhage rate

A more popular use of SRS is to reduce the risk of future hemorrhage and consequential neurological deterioration, especially for deep-seated lesions. The first
CHAPTER 9 • Radiosurgery for cerebral cavernomas

Critical considerations on cavernoma radiosurgery

The lack of radiological proof of cure after treatment is the major pitfall of CCM SRS that keeps skepticism alive. The problem is not only the fact that these lesions are angiographically occult, but MRI also fails to demonstrate a definite change in the appearance of the lesion after SRS. Although the proportion of true growth is somewhat higher in untreated population,23, 33, 50, 66, 76, 78 MRI-appearance of CCMs after SRS is statistically as heterogeneous as without treatment. Approximately half of the lesions shrink,75, 76 but post-radiosurgery shrinkage may in part be due to resolution of intra-lesional hematomas. Thus, in contrast to AVMs, it

Table 9-I.—Summary of CCM series using modern gamma-radiation based SRS (the latest report from each group).

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients/lesions (N.)</th>
<th>Deep (N)</th>
<th>Superficial (N)</th>
<th>Marginal (prescription) dose (Gy)</th>
<th>Gross target volume (cm³)</th>
<th>Post-treatment 1st bleed (year)</th>
<th>Pre-treatment bleed (year)</th>
<th>Post-treatment bleed until 2yr (year)</th>
<th>Post-treatment bleed after 2yr (year)</th>
<th>Permanent ARE (%)</th>
<th>Post-treatment bleed related morbidity (%)</th>
<th>Mortality related to treated CCM (%)</th>
<th>Treatment years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kida &amp; Hasegawa 2004 †</td>
<td>152</td>
<td>87</td>
<td>65</td>
<td>14.9</td>
<td>N/A</td>
<td>31.8</td>
<td>8**</td>
<td>&lt;5</td>
<td>N/A</td>
<td>2</td>
<td>1991-2001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu et al. 2005 ‡</td>
<td>125</td>
<td>63</td>
<td>49</td>
<td>12.1</td>
<td>3.12</td>
<td>N/A</td>
<td>29.2</td>
<td>10.3</td>
<td>3.3</td>
<td>2.5</td>
<td>9.6</td>
<td>1993-2002</td>
<td></td>
</tr>
<tr>
<td>Kida 2009 ††</td>
<td>84</td>
<td>84</td>
<td>0</td>
<td>13.4</td>
<td>N/A</td>
<td>N/A</td>
<td>7.1</td>
<td>1.8</td>
<td>N/A</td>
<td>2.4</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al. 2010 †</td>
<td>96</td>
<td>13</td>
<td>83</td>
<td>15.6</td>
<td>N/A</td>
<td>N/A</td>
<td>4.2</td>
<td>&lt;2.1</td>
<td>N/A</td>
<td>5.2</td>
<td>N/A</td>
<td>1995-2005</td>
<td></td>
</tr>
<tr>
<td>Lunsford et al. 2010 ††</td>
<td>103</td>
<td>93</td>
<td>16</td>
<td>1.1</td>
<td>3.6</td>
<td>N/A</td>
<td>32.5</td>
<td>10.8</td>
<td>1.06</td>
<td>1</td>
<td>N/A</td>
<td>1989-2005</td>
<td></td>
</tr>
<tr>
<td>Monaco et al. 2010 ††</td>
<td>68</td>
<td>68</td>
<td>0</td>
<td>1.1</td>
<td>3.8</td>
<td>N/A</td>
<td>32.38</td>
<td>8.2</td>
<td>1.37</td>
<td>1.5</td>
<td>N/A</td>
<td>1988-2005</td>
<td></td>
</tr>
<tr>
<td>Nagy et al. 2010 ‡</td>
<td>113/118</td>
<td>118</td>
<td>0</td>
<td>12-15</td>
<td>0.26-0.61</td>
<td>2.2***</td>
<td>5.1</td>
<td>1.3</td>
<td>7.3</td>
<td>7.3</td>
<td>0</td>
<td>1995-2008</td>
<td></td>
</tr>
<tr>
<td>Lee et al. 2012 ‡</td>
<td>49/50</td>
<td>50</td>
<td>0</td>
<td>11</td>
<td>3.2</td>
<td>N/A</td>
<td>31.3</td>
<td>3.5</td>
<td>1.74</td>
<td>4.1</td>
<td>N/A</td>
<td>0</td>
<td>1993-2010</td>
</tr>
<tr>
<td>Jay et al. 2012 †</td>
<td>16</td>
<td>16</td>
<td>0</td>
<td>13</td>
<td>0.42</td>
<td>N/A</td>
<td>35.72</td>
<td>3.59</td>
<td>0</td>
<td>0</td>
<td>6.25</td>
<td>1998-2009</td>
<td></td>
</tr>
<tr>
<td>Park &amp; Hwang 2013 ‡</td>
<td>20</td>
<td>20</td>
<td>0</td>
<td>13</td>
<td>0.56</td>
<td>N/A</td>
<td>39.5</td>
<td>8.2</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>2005-2010</td>
<td></td>
</tr>
<tr>
<td>Liscak et al. 2015 ‡</td>
<td>112</td>
<td>50</td>
<td>62</td>
<td>0.9</td>
<td>N/A</td>
<td>N/A</td>
<td>3.2</td>
<td>0.5</td>
<td>0.9</td>
<td>3.6</td>
<td>2.7</td>
<td>1992-2000</td>
<td></td>
</tr>
<tr>
<td>Frischer et al. 2014 ‡</td>
<td>38</td>
<td>38</td>
<td>0</td>
<td>12</td>
<td>0.3</td>
<td>N/A</td>
<td>7.2</td>
<td>2.63</td>
<td>0.6</td>
<td>7.9</td>
<td>N/A</td>
<td>1987-2011</td>
<td></td>
</tr>
<tr>
<td>Lee et al. 2014 ‡</td>
<td>49</td>
<td>49</td>
<td>0</td>
<td>13.1</td>
<td>0.74</td>
<td>N/A</td>
<td>38.36</td>
<td>9.84</td>
<td>1.5</td>
<td>2</td>
<td>N/A</td>
<td>1992-2011</td>
<td></td>
</tr>
<tr>
<td>Kim et al. 2014 ††</td>
<td>39</td>
<td>39</td>
<td>0</td>
<td>13</td>
<td>1.1</td>
<td>N/A</td>
<td>53.6***</td>
<td>8.1</td>
<td>2.4</td>
<td>0</td>
<td>N/A</td>
<td>1997-2012</td>
<td></td>
</tr>
<tr>
<td>Azimi et al. 2015 ††</td>
<td>100</td>
<td>74</td>
<td>26</td>
<td>13</td>
<td>1.5</td>
<td>N/A</td>
<td>34.3</td>
<td>4.1</td>
<td>1.9</td>
<td>N/A</td>
<td>0</td>
<td>2003-2011</td>
<td></td>
</tr>
<tr>
<td>Fedorcsák et al. 2015 ††</td>
<td>45/51</td>
<td>14</td>
<td>37</td>
<td>14</td>
<td>1.38****</td>
<td>N/A</td>
<td>1.53</td>
<td>0.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2008-2012</td>
<td></td>
</tr>
</tbody>
</table>

ARE: adverse radiation effect, N/A: not applicable. *During 5 years prior to radiosurgery. **First year after treatment. ***First no more than one bleed, second line multiple bleeds prior to SRS. ****Only 5 of 39 patients had bled twice prior to SRS. *****First line deep-seated, second line superficial. †, ‡, ††: Data from the same groups analyzing either both deep-seated and superficial, or brainstem lesions only. All except one group used Gamma Knife®, the one exception used GammaRT-6000™.50

report of large clinical series using modern SRS technique with sufficient follow-up time published in 1995 found that rebleed rate fell from 32%/patient/year pre-treatment to 8.8 within the first 2 years after treatment and to 1.1 thereafter.1 Contemporary SRS studies either focusing on deep eloquent lesions45, 66-73 or studying mixed population of superficial and deep-seated CCMs50, 62, 63, 74-77 found similar drop in rebleed rates within a latency period of 2-3 years (Table 9-I).
is impossible to tell radiologically of an individual CCM whether it is secure from further bleed or not. Moreover, AVMs and CCMs differ both in terms of pathobiology and histopathology, and the only comparative study demonstrated – beside similarities – different histopathological effect of SRS on AVMs and CCMs. Due to the lack of exact measure for cure, we can only rely on statistical evaluation of clinical data and a prospective randomized controlled trial to clarify the conflicting issues surrounding SRS may appear attractive. However, it is unlikely to realize such a trial in the near future for numerous reasons, particularly due to the widely different immediate impact of the 3 management options that would limit enrolment. We and others have therefore recently suggested international prospective registries including all detected cases regardless of subsequent choice of management modality. Until such data arrive, to answer critical voices addressing both effectiveness and safety of CCM SRS, it is crucial to define standard SRS data collection (Table 9-II) and modern treatment protocol both for critical review of current literature and for future data publication.

Regarding clinical outcome the first line of criticism addresses effectiveness of SRS. Admittedly, not all published studies demonstrated reduction in rebleed rate of CCMs after the widely accepted 2-year latency period: temporary increase in rebleed rate was also reported as well as reduction of rebleed rate after a longer latency period. We have alluded to the difficulties interpreting hemorrhagic events, particularly when attempts are made to account for pre-diagnosis clinical events: these exceptions may reflect the varied interpretation of what counts a hemorrhage and may well be due to different patient selection. As also mentioned above, the key for proper interpretation of CCM SRS is the distinction between the risk of first and repeated hemorrhage, as well as between hemispheric and deep-seated lesions. Analyzing exclusively the results of SRS for deep eloquent CCMs that had bled at least twice prior to treatment (i.e. proven to behave more aggressively), we consequently find a sharp drop in annual rebleed rate from about 30% to 1-2% within 2 years after treatment. When confining analysis exclusively to SRS for CCM that had bled no more than once prior to treatment, during the first 2 years after SRS a higher rate of hemorrhage may be found when compared to first ever hemorrhage rate. Importantly, this is rebleed (the rate being still much lower than rebleed rate of untreated lesions expected in a mixed population of CCM with more aggressive and benign nature) and therefore the increase is relative to first ever bleed rate. It

Table 9-II.—Proposal for reporting standards for radiosurgery of CCMs. [Modified from Nagy G et al.]

<table>
<thead>
<tr>
<th>Patient and lesion characteristics prior to treatment</th>
<th>Patient and lesion characteristics prior to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation and treatment</td>
<td>Sex, family history</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td>Persisting deficits (modified Rankin Score – mRS)</td>
</tr>
<tr>
<td>Multiplicity</td>
<td>Rate of first bleed and rebleed (/treated lesion/year)</td>
</tr>
<tr>
<td>公布</td>
<td>裂0, 1 or ≥2 (to be analyzed separately)</td>
</tr>
<tr>
<td>Location: superficial/deep-seated (to be recorded separately)</td>
<td>Non-hemorrhagic clinical events</td>
</tr>
<tr>
<td>Treatment parameters</td>
<td>Gross target volume (GTV)</td>
</tr>
<tr>
<td>Prescription isodose volume (PIV)</td>
<td>Marginal (prescription) dose</td>
</tr>
<tr>
<td>Volumes receiving 10 and 12 Gy</td>
<td>Post-treatment hemorrhage rates (/treated lesion/year)</td>
</tr>
<tr>
<td>≤2 years</td>
<td>&gt;2 years after treatment</td>
</tr>
<tr>
<td>Morbidity related to post-treatment hemorrhages (as drop in mRS)</td>
<td>Morbidity related to radiation (ARE)</td>
</tr>
<tr>
<td>Temporary (duration, requirement for medication)</td>
<td>Persisting (as drop in mRS)</td>
</tr>
<tr>
<td>Radiology (if applicable)</td>
<td>Radiology (if applicable)</td>
</tr>
</tbody>
</table>

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is also important to note that the rate of further bleed after the 2-year latency period is minimal even in this population. Recent debate on the effect of SRS on CCM hemorrhage rate is centered on whether the fall of rebleed rate within 2 years can really be attributed to the radiobiological effect of the treatment or whether it simply reflects natural history, as hemorrhages may occur in clusters that was suggested by some observational studies.\textsuperscript{37, 41, 42} Such a coincidence after SRS seems unlikely as several observations indicate increased rebleed rate for much longer time period if untreated,\textsuperscript{29, 43-45} and the time course of reduction in rebleed rates after SRS parallels the time course of histological changes observed after irradiation.\textsuperscript{60} As current radiosurgical literature lacks untreated control group,\textsuperscript{2} this debate will be speculative until such data arrive.

The other major concern addresses safety of SRS. Early studies, often cited by critics, reported high radiation-associated complication rates (adverse radiation effects, AREs). However, those studies were from an era with poor delineation of the target with CT or less conformal MRI, and with the use of higher dose protocols that came from historic AVM-experience.\textsuperscript{6-8, 56} Clearly, these studies represent the early experimental phase of the collective learning curve of CCM SRS. On the other hand, modern studies applying the following treatment protocol have reported low rates of AREs resulting in only low rate of mild persisting morbidity without mortality attributed to radiation (Table 9-I). We experienced such a learning curve in Sheffield, from early attempts resulting high rate of AREs until we adopted contemporary treatment protocol that dramatically decreased the rate and severity of AREs.\textsuperscript{15} Contemporary technique uses prescription dose less than 20Gy (typically 12-15), highly conformal MRI-based treatment planning and treating only lesions without evidence of recent bleed (Type II or III,\textsuperscript{23} at least 3 months after last hemorrhage) (Figure 9.2). It seems also crucial that the lesion should be defined strictly within the hemosiderin ring that is speculated to be radiosensitizer (Figure 9.2C).\textsuperscript{81} Associated DVAs should also be preserved (similarly to microsurgery\textsuperscript{52}), because irradiating them (as closing them with microsurgery) was found to be associated with high rate of complications.\textsuperscript{82}

\textbf{Figure 9.2.}—A) Treatment planning on T1-weighted MR image of a type II pontine CCM; B) treatment planning on T2-weighted MR image of a type II left thalamic CCM; C) larger view of the plan seen in B) to demonstrate the highly conformal plan and prescription isodose line within the hemosiderin ring. Yellow line: 50\% (prescription) isodose line. Green line: 8 Gy line.
Critical review of radiosurgical literature

The disappointingly heterogeneous quality of literature on CCM SRS with distinct measures of natural history, post-treatment bleed rates and ill-definition of treatment standards provides ammunition for the critics who often cite early experimental and low quality contemporary studies that would support their negative view. Critical review of the literature and improved data collection with standardized reporting (Table 9-II) and treatment criteria seems to be the most realistic way to get a better view on safety and effectiveness until high level evidence becomes available.11

First, for clear distinction between hemorrhagic and non-hemorrhagic clinical events, the definition of clinical hemorrhage should be standardized in all future papers published on CCM field, as suggested earlier.24 Retrospective annual first bleed rate for treated lesions (/lesion/year) should be recorded separately to annual rebleed rate until treatment, and hemorrhage rates should also be calculated separately within 2 years post-treatment and thereafter. In our view, it is crucial to analyze separately superficial and deep-seated lesions, and lesions with 0, 1 or multiple bleeds, due to their disparate natural history. Although causal relationship with SRS is not proven for all cases, all lasting neurological deterioration unrelated to a post-treatment hemorrhage should be considered as adverse radiation effect, in order to determine the maximal potential morbidity of SRS. Due to delayed protection that is specific to this treatment modality, morbidity related to post-treatment hemorrhage should also be recorded accurately. For a contemporary treatment protocol a gamma-radiation based instrument appears to be the most precise SRS treatment due to its highest conformity achieved with multiple isocenters, owing to the lowest extratransional radiation dose and the largest experience accumulated worldwide.

Only few systemic reviews dealing with CCM SRS have been published, and none of them meet the above criteria because they typically pooled studies of heterogeneous quality. Surgical reviews usually support a negative view referring to early SRS reports.9, 46, 47 A recent systemic review applying criteria of modern evidence based medicine found only one study comparing SRS to surgery and one comparing SRS to observation.2 However, both studies represented early attempts with poor definition of natural history, selection criteria and follow-up. A detailed extensive meta-analysis has pooled all available SRS studies published until 2009 without distinction on natural history, anatomical location, and SRS technique.16 As large modern SRS series have been published since then, this study unavoidably underestimates its effectiveness with overestimation of its morbidity. Another recent study has specifically focused on SRS of brainstem CCMs analyzing 5 series.37 Of these, only 3 would meet the above strict methodical criteria.67, 68, 70 The most recent, very detailed descriptive systemic review has compared outcomes of surgical and radiosurgical interventions.15 However, as it is clear from the data provided the ratio of hemispheric and deep eloquent, as well as hemorrhagic and non-hemorrhagic lesions is different between the two groups, reflecting on different patient populations. Comparing the effect of these two interventions on two distinct group of patients does not seem appropriate.

All modern radiosurgical series (listed in Table 9-I) are retrospective and lack control groups. However, by analyzing them in terms of effect on hemorrhage rate and morbidity, there is a strong suggestion that SRS is an apparently effective and safe treatment method.
Hemorrhage

For pragmatic reasons the minimal definition of clinical hemorrhage is a new clinical event associated with imaging evidence of hemorrhage. However, over half of the listed studies fail to define what they count as hemorrhage. Moreover, the lack of distinction between deep-seated and superficial CCMs, and between first and repeated bleed makes it hard to form a definitive conclusion regarding the real effect of SRS on hemorrhage rate. Owing to these difficulties, we found only 5 papers that could be used for calculating rebleed rates in deep-seated lesions with multiple hemorrhages prior to SRS. Based on these papers, annual rebleed rate falls from 32.26% pre-treatment (95% CI: 29.15-35.37; 281 repeated hemorrhages in 871 person-years) to 8.28% within the first 2 years after SRS (95% CI: 5.27-11.29; 27 repeated hemorrhages in 326 person-years), and to 1.51% thereafter (95% CI: 0.53-2.5; 9 repeated hemorrhages in 595 person-years) (N.=197).45, 67, 68, 70, 72 Moreover, only two studies analyzed separately those deep-seated CCMs that had had bled not more than once prior to SRS finding that annual rebleed rate stabilized at 1.6% (95% CI: 0.03-3.17; 4 repeated hemorrhages in 250 person-years) after a 2-year period of temporary increase to 5.71% (95% CI: 2.24-9.49; 10 repeated hemorrhages in 175 person-years) (N.=108).45, 72

Morbidity after radiosurgery

As the beneficial effect of SRS is expected only after a latency period and the risk of hemorrhage never seems to reach zero, post-treatment hemorrhage may also add to persisting morbidity. In those 6 studies where this was mentioned, 5.66% of patients suffered persisting neurological deficit due to hemorrhage after SRS (95% CI: 3.41-7.92; N.= 406).45, 50, 62, 69, 70, 76 Persisting morbidity related to post-treatment bleed was similar (5.3%), when we included only deep-seated lesions (95% CI: 1.43-9.18; N.=132).45, 50, 69, 70 Mortality related to treated CCMs was 0.84% (95% CI: 0.26-1.41; N.=958), and was exclusively caused by post-treatment hemorrhage, or was related to surgical removal after rebleed. Once suffering from a bleed, the likelihood of permanent deficit seems to be the same with post-treatment hemorrhages as with pre-treatment hemorrhages, suggesting that the benefit of SRS is not to reduce the severity but the frequency of the bleed.45 Perilesional edema, causing temporary neurological deficit or remaining clinically silent, is typically seen within 12 months after SRS. Persisting AREs typically present later, their rates are low, 4.16% (95% CI: 2.09-6.22%, N.=376) in deep-seated lesions, resulting in only mild disability.45, 50, 67-69, 71-73 The rate of persisting morbidity for hemispheric lesions is even lower, 0.82% (95% CI: 0-2.44%, N.=122).50, 62, 75

Directions in modern management of cavernomas

Three management options can be considered for a CCM: microsurgical removal, SRS and observation. Currently there is no consensus for the role of these 3 modalities in CCM management due to the lack of quality evidence,3 although it appears that despite the overlap between indications, the 3 are not competitive but complementing each other. Based on available data we have recently recommended a treatment algorithm (Figure 9.3).11 However, it is important to note that the final decision should be made on an individual basis taking into account not only CCM
Figure 9.3.—Proposed algorithm for the management of CCMs.

* Surgery is first option in most cases, but SRS is a valid alternative. ** Both modalities appear to be effective, but currently there is no evidence to demonstrate superiority of either. Modified from Nagy G et al. Examples of typical scenarios are illustrated in Figure 9.4.

location and behavior, but age, and medical condition. Moreover, the final treatment decision is also influenced by neurosurgeon’s experience and the preference of the fully informed patient. Surgery for symptomatic superficial CCMs is usually safe and effective, while incidental hemispheric lesions can be observed due to the low chance of resulting persisting morbidity. For deep-seated lesions surgical removal is generally recommended only in limited circumstances in experienced hands. Lesions with the history of repeated hemorrhages causing progressive neurological deficit or significant mass effect should either reach the pial or ependymal surface or should be approachable through a non-eloquent surgical corridor. The risk of surgical removal of CCMs located in the brainstem or thalamus/basal ganglia is still substantial even in experienced hands, resulting in 10-14% persisting morbidity and 1.5-1.9% mortality, with 89-91% resection rate. Importantly, rebleed rate never goes to zero even after microsurgical removal due to the proportion of residual lesions, 62% of which rebleed with an annual rate of 0.5-2% and with 6% mortality. Thus, though an effective salvage treatment, surgical removal is generally not considered as a prophylactic measure in patients harboring deep-seated CCM with no or minimal neurological deficit. The question for these lesions is whether to observe or treat them with SRS (Figure 9.4). Since the introduction of modern CCM SRS in 1995 we treated 314 lesions at the National Centre for Stereotactic Radiosurgery in Sheffield until 2012, 191 of them being deep-seated. When we reviewed our data in 2010 we found that two third of the treated deep-seated lesions had had not more
than one bleed prior to SRS in our material and the annual bleed risk stabilized at a low rate after the expected two year latency period. Since then similar results have been published by another group. These data, together with concordant results from numerous groups using modern SRS technique on deep-seated CCMs with multiple hemorrhages imply that SRS is an effective and safe treatment. Thus, increasing experience reassures us in our policy that it is not justified to wait for another bleed and the resulting cumulative morbidity when a safe and apparently effective non-invasive treatment method for deep-seated CCMs is available.

**Conclusions**

SRS for CCM has gained wide acceptance especially during the last decade. This may be in large part due to better imaging, the evolution of radiosurgical techniques
and to our better understanding of the natural history despite their heterogeneous and unpredictable nature. SRS for this indication evolved from experimental attempts treating aggressive inoperable lesions to becoming an attractive treatment modality, especially for deep-seated lesions soon after first presentation in order to prevent further clinical deterioration caused by repeat hemorrhage. Undoubtedly, particularly during the last few years it has been considered to complement microsurgery and wait-and-see policy as increasing number of publications using modern treatment protocols pointing to very similar outcome direction are available. We acknowledge that SRS in the management of CCM remains controversial due to the lack of high level evidence. However, as there is now sufficient positive experience supporting the use of SRS for CCM located in the brainstem, thalamus, basal ganglia, or internal capsule, once they become symptomatic, we feel that inactivity is no longer justified.85 Furthermore, due to the recognized cumulative morbidity of repeated hemorrhages on one hand and the low risk of radiation induced adverse effects on the other, we advocate an early intervention 3-6 months after the first bleed (once the patient has recovered and hematoma resolved). The “CCM controversy” may remain the subject of debate until after further studies this treatment wins its right place in the neurosurgical armamentarium.

References