Radiotherapy in cavernous malformations: anatomy of a controversy

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The invitation to write an editorial on the article by Lunsford et al.19—“Stereotactic radiotherapy for symptomatic solitary cerebral cavernous malformations considered high risk for resection”—published in this issue of the Journal of Neurosurgery provided the opportunity for rigorous scrutiny of both our and Lunsford’s role in this controversy. We looked for possible flaws: biases and the quest to prevail, rather than the pursuit of truth, which might have tainted the approach to the issue. A short narrative of the start and the development of the dispute may make it easier to understand the controversy’s resilience.

Our successful obliteration of a series of cerebral arteriovenous malformations using the Gamma Knife in the 1970s26,27 prompted a trial using the same technique for cavernous malformations (CMs). Between 1983 and 1987 Steiner treated 15 cases, and the unexpected unfavorable outcomes were first reported on April 30, 1990, in an oral presentation at the American Association of Neurological Surgeon’s Annual Meeting in Nashville, Tennessee.11 Lunsford et al.19 started using the Gamma Knife for CMs in 1988, and Coffey from Pittsburgh, commenting on our presentation,31 explained our bad results based on the use of CT imaging instead of MR imaging (unavailable in Stockholm at that time) and too-high prescription doses. Steiner decided on a total moratorium on radiotherapy for CMs, which Karlsson, Kihlström, Rähn, and Noren implemented in Stockholm only after unsatisfactory outcomes in an additional 8 patients treated between 1990 and 1996.8 Lindquist treated another 4 brainstem and 1 thalamic CM at Bupa Cromwell Hospital in London. Despite low prescription doses in the latter 2 series (10–16 Gy) and the use of MR imaging for dose planning, the results were not better than for the first 15 cases. The follow-up for the cases treated in London was 6–27 months.

Rebleeding after radiotherapy occurred in 2 cases, and radiation-induced complications were noted in another 2 cases. One case remained unchanged with moderate neurological deficits.

Kondziolka et al.15,16 published 2 articles: 1 prospective study assessing the natural course of CMs and 1 retrospective study suggesting that radiotherapy protects CMs from rupture. These authors later reported long-term results emphasizing an improvement in the natural history of CMs following radiotherapy and advocating radiotherapy in cases of difficult approaches for microsurgery.8,14,15 An increasing number of neurosurgeons followed the policy established in Pittsburgh without any reservation.20,17 Others did so but with some caveats.1,12,22 Pollock and colleagues22 stated that “limitations in our knowledge of the natural history of untreated CMs make it impossible to conclude that radiotherapy protects against the future risk of bleeding. Radiotherapy of CMs does appear to entail a greater risk of radiation-related complications compared with that of [arteriovenous malformations].” Huang et al.,7 commenting on the impressive results of Hasegawa and associates,5 emphasized selection bias as well as the difference between hemorrhage and outcomes described by him as compared with those previously reported. Huang and colleagues also criticized the use of the study group as its own control. Friedman’s complimentary review of the same paper was tempered by the same critical mention of selection bias.5

We described both an occasional limited decrease in the hemorrhage rate after radiosurgical treatment and partial obliteration of a CM excised by Steiner when 5 years after a Gamma Knife procedure no improvement in the frequency of seizure had been achieved (Fig. 1).8,28,29 but we believed that the high incidence of radiation-induced complications did not justify the limited protection the treatment might afford. We suggested, “a prospective randomized study is needed to establish the role of radiosurgery in the management of these lesions.”8

The most revealing part of the current report by Lunsford et al.19 is the candid account of the study’s weaknesses. In their Discussion, while emphasizing that they did not observe in their material any clustering of bleeding such as that reported by Barker et al.,7 they did admit that their “data cannot refute the hypothesis that some CCMs may bleed repeatedly for some interval and then cease to bleed—a possibility that could prove to be a confounding variable at odds with our results.” Lunsford and colleagues also agree that the results of the retrospective method they used may have been partly skewed.
Studies analyzing the natural course of CMs are either prospective or retrospective. Retrospective studies can be divided into 2 groups depending on the methodology used. With Method A, one simply divides the number of observed hemmorhages by the number of risk years. This method assumes that the patients are born with CMs and that the annual risk for hemorrhage is constant. In Method B, the number of observed hemmorhages is divided by the number of risk years as well, but both values are from the day after the first hemorrhage. Thus, the first hemorrhage as well as the time at risk before the first hemorrhage is excluded, making the method insensitive to the time of the development of the CM.

Retrospective studies document the incidence of hemorrhage, which may or may not equal the prospective risk for hemorrhage. A selection bias can lead to a significant difference between the found incidence of and the actual annual risk for hemorrhage. The likelihood of drawing skewed conclusions is very high should the patient selection be based on prior ruptures. The impact of this selection bias is much weaker in prospective studies, making reasonable the assumption that the calculated incidence of hemorrhages equals the actual risk for hemorrhage.

The annual risk of hemorrhage in 4 published studies analyzing the natural history of CMs is provided in Table 1. The incidence of hemorrhage using prospective methods ranged between 0.8 and 3.8%. The incidence calculated from the same group of patients ranged between 0.3 and 2.3% if Method A was used. The minimal difference can be explained by the way patient-years at risk are calculated. In Method A one assumes that patients were born with CMs, which might not be true because the low incidence of hemorrhage in children and de novo CMs in familial CMs contradicts this assumption. Because the natural course of CMs is still poorly understood it is tempting to use the pretreatment incidence of hemorrhage in the treated patient population as an indicator of the pretreatment risk instead of the 0.3–3.8% annual risk documented in papers analyzing the natural course of CMs. The argument that CMs in the treated patient population represent a higher risk for hemorrhages than other CMs—the proof being that they frequently bled before treatment—sounds like circular reasoning to us and may lead to erroneous conclusions.

In Table 2 we analyzed the annual risk of hemorrhage in radiosurgical series of patients with CMs, which selected only so-called high-risk patients. Using Method A, hemorrhage rates in these high-risk patients ranged between 3.9 and 6.5%, a little higher than the reported rates of 0.3–3.8% in the studies of natural history, but they became 17–36% when Method B was used. Can this difference be explained by a much higher hemorrhage risk among patients selected for radiosurgery, or is it mainly caused by a methodological flaw? If we agree that the higher risk of subsequent hemorrhages for some period of time occurs in patients with prior symptomatic hemorrhages, the calculation of the hemorrhage rate using Method B will be problematic, because the increased number of hemorrhages at this specific time period and the prematurely terminated follow-up time by radiosurgery lead to a skewed, overly high hemorrhage rate.

Increased Hemorrhage Risk for Some CMs

Available evidence suggests that CMs are not static lesions for which the risk of a clinically detectable hemorrhage is constant and independent of anatomical and clinical factors. It has been suggested that the risk for hemorrhage is higher in female patients and in centrally located CMs. Kondziolka et al. have also observed that the risk for a clinically detectable CM hemorrhage increases after an earlier bleed; however, it is unknown for how long this elevated risk persists. It is reasonable to believe that the increase in risk is temporary; if not, a larger number of CMs would have a higher risk for hemorrhage because the majority of these lesions show imaging evidence of either acute or subacute hemorrhage. It should also be noted that while blood degradation products suggest prior hemorrhages, they might also occur from extravasations of a small amount of erythrocytes.

To our knowledge, the duration of the increased risk has not been analyzed in any scientific publications; therefore, we cannot exclude the possibility that the decrease in the bleeding rate after the treatment of recently hemorrhaged CMs is to some extent caused by a reset to the prehemorrhage bleeding risk rather than by treatment.