EDITORIAL

Radiosurgery and cavernous malformations

Jason Sheehan, MD, PhD,1,2 Dale Ding, MD,1 and Robert M. Starke, MD1

Departments of 1Neurological Surgery and 2Radiation Oncology, University of Virginia, Charlottesville, Virginia

The successful obliteration of selected cerebral arteriovenous malformations (AVMs) using the Gamma Knife prompted the treatment of cavernous malformations (CMs) and aneurysms. For CMs, their small volume, lack of intervening normal brain tissue, and relatively low rate of clinically significant hemorrhage made them an appealing target for stereotactic radiosurgery (SRS). Radiosurgery for aneurysms was quickly abandoned as a failure, but radiosurgery for CMs persists despite controversy regarding its therapeutic value.13

Unlike for AVMs, radiosurgery for CMs often appears to have little to no effect evident on follow-up neuroimaging studies. In a previous report, a CM treated with Gamma Knife radiosurgery appeared unchanged on follow-up MRI 5 years afterwards.13 Extirpation of the lesion was undertaken, and histological examination revealed the lesion was partially obliterated with patency to a single persistent capillary channel (Fig. 1). Therefore, the correlation between radiographic and pathological changes may be unreliable following CM radiosurgery.

From a series of more than 100 CMs treated at the University of Pittsburgh, Shin and colleagues report on the histopathological responses of 4 patients with CM who underwent resection 4 months to 7 years following radiosurgery.10 The CMs were treated with prescription doses of 14–15 Gy of radiation. In all 4 cases, radiosurgery failed and the patients suffered recurrent hemorrhages. Histopathological analysis revealed partially obliterated vessels and incomplete sclerosis as early as 4 months following radiosurgery. Partial obliteration could be a response to repeated microbleeds, recent hemorrhage, or past radiosurgery. Foci of neovascularization were also observed, as evidenced by staining for vascular endothelial growth factor (VEGF).

In the case from our institution as well as the 4 from the University of Pittsburgh, we run the risk of drawing too much significance from a small and undoubtedly biased cohort. Nevertheless, the findings from Shin et al.’s study are some of the best available for elucidating the underlying radiobiological changes from radiosurgery on CMs. Coupling these histopathological findings with the neuroimaging and clinical outcomes published in the literature, it would seem safe to conclude that radiosurgery induces some of the same vessel sclerosis in CMs as it does in AVMs. However, the changes in AVM compared to CM vasculature following radiosurgery are substantially more robust and complete in the majority of patients.13,15,12 The incomplete response seen in CMs after radiosurgery may explain the potentially lower but still tangible risk of recurrent hemorrhage (8.8% annual risk for the first 2 years, then 1.1% annual risk after 2 years based on the group’s prior publication) in patients even years after radiosurgery.6 In contrast, in more than 1400 AVM patients treated using SRS, we have not observed a single hemorrhage in an AVM confirmed to be obliterated on angiography.11

The incomplete histopathological changes in CMs are consistent with the reduced but persistent risk of hemorrhage following radiosurgery.

These findings raise 2 potential options for improving CM radiosurgery outcomes. First, the 4 patients in the current series were treated with a radiosurgical dose of 14–15 Gy to the margin of the CM. Prior preclinical and clinical studies have demonstrated more beneficial vascular changes with higher doses.1,5,7 However, such higher doses in patients with CM have also been associated with more complications. For example, in an early cohort of 22 CM patients treated with a mean margin dose of 18 Gy, 6 patients suffered neurological decline due to radiation-induced changes, and 5 (22.7%) had permanent deficits.4 Radiation-induced complications were defined as necrosis or transient radiation-induced changes demonstrated on CT or MRI and associated with a neurological decline. The radiation-induced complication rate in CMs was more than 2 times higher than expected for a simi-
FIG. 1. An immunohistochemical section depicting a CM, which was treated with radiosurgery. The lesion was excised 5 years after stereotactic radiosurgery. With the exception of a single persistent capillary channel (arrow), the CM appears obliterated. This image was published in Operative Neurosurgical Techniques: Indications, Methods, and Results, fifth ed., Steiner L, Sheehan J, Lindquist C, Stroila M, Steiner M, Gamma surgery in cerebral vascular lesions, malformations, tumors, and functional disorders, pp 530–576, Copyright Elsevier, 2006.

larly treated group of patients with AVM. An increased incidence of radiation-induced changes following CM radiosurgery has been described by others, and the risk appears related at least in part to the margin dose. Thus, a higher dose alone for CMs may provide improved vascular occlusion, but conveys a greater risk of adverse radiation effects. Given the VEGF expression seen in these CMs, a target VEGF inhibition (for example, bevacizumab). Vascular endothelial growth factor inhibition may serve to potentiate the effects of radiosurgery and lower the risks of radiation injury to adjacent brain tissues, thereby allowing a higher margin dose to be delivered to CMs. It may also downregulate neovascularization in the CM following irradiation.

In conclusion, the authors have shed substantial light on the histopathological changes that follow radiosurgery for CMs. These findings point toward areas for refinement of the radiosurgical approach. Until then, we recommend reserving radiosurgery for carefully selected CM patients suffering from repeated seizures, hemorrhages, or progressive neurological deficits and for whom the risks of resection are deemed unacceptably high.

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References

Response
Samuel S. Shin, MD, PhD, L. Dade Lunsford, MD, and Robert M. Friedlander, MD

Department of Neurological Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

As we have reported in a prior publication, our experience indicates that SRS for CMs in patients with repeated bleeding reduces subsequent bleed rates, a finding that becomes quite clear after the initial 2 years. However, there is still room for improvement in further reducing re-hemorrhage rates. The pathological response of CMs to SRS is similar to what is seen in AVMs but perhaps not as robust as described in the current histological analysis as well as several prior studies. This result may be related to the dose reduction to improve the safety profile. In patients with CM, perilesional iron deposition associated with prior bleeding events acts as a relatively potent radiation sensitizer. The radiosurgical target must be confined by highly selective delivery of the focused radiation within the hemosiderin ring defined on T2-weighted MRI. To provide more complete obliteration of CM, a strategy
of sensitizing CM to radiation or increasing the radiation dose without adversely affecting adjacent critical brain structures would be useful.

Sheehan et al. emphasize an excellent point regarding the potential development of agents that can enhance CM radiosurgery outcomes. The current study shows that VEGF and angiogenesis may have a major role in the continued pathogenic vasoproliferation of CM even years following SRS. We have previously described the use of bevacizumab (VEGF inhibitor) in the setting of radiosurgery. This drug has also been shown to be effective in reducing adverse radiation effects in tumors as well as vascular malformations. These prior studies focused on the use of bevacizumab to reduce the role of VEGF as a cytokine mediator of radiation injury. Vascular endothelial growth factor is probably one of the primary mediators of peritumoral edema and is found in high concentrations in reactive astrocytes in necrotic tissues. However, its use in delayed angiogenesis of CM treated with SRS has not been explored. The use of bevacizumab for CMs can serve 2 functions: 1) reducing adverse radiation effects by allowing higher radiation doses, and 2) preventing additional angiogenesis of CMs.

The strategy of combining radiation techniques with antiangiogenic agents has been applied to a variety of pathologies. This strategy has shown promising results in animal models as well as clinical trials of head and neck cancers, lung cancer, and hereditary hemorrhagic telangiectasia. Similarly, clinical and preclinical trials using radiation therapy combined with various vascular disrupting agents have been reviewed. These agents combined with radiosurgery may provide significant improvement in outcomes for CMs treated with SRS.

Currently, SRS is used for patients with multiple bleeds (high rebleeding rates) and whose CMs are located in brain regions where the access route may pose an excessive risk of new permanent neurological injury. Further developments of pharmacological agents that improve the effectiveness of SRS may facilitate a reduction in complications and increase success rates.

References