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## Stereotactic Radiosurgery for Management of Cavernous Malformations

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# Stereotactic Radiosurgery for Management of Cavernous Malformations

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Cavernous malformations (CMs) are abnormal vascular formations of the brain with an estimated incidence of 0.4%-0.8% in the general population.<sup>1</sup> CMs have the potential to cause significant morbidity, and have been associated with epileptic seizures, intracranial hemorrhage, and focal neurological deficits.<sup>2</sup> Management options include non-treatment, surgical resection, and radiosurgery. We review here the efficacy of different management strategies for cavernous malformations and highlight the specific role of radiosurgery.

One of the major complications of cerebral cavernous malformations is intracranial hemorrhage. To optimize patient treatment, it is beneficial to be able to identify patients that are at an increased risk of developing a hemorrhage and would most benefit from intervention. The overall rate of hemorrhage in patients with CMs has been estimated to be 2.25%.<sup>3</sup> The rate of hemorrhage, however, is significantly affected by the initial symptom presentation. Patients presenting with a hemorrhage have significantly higher rates of rehemorrhage compared to patients presenting due to incidental findings.<sup>3,4</sup> Flemming et al. found that patients presenting with hemorrhage had an overall annual rate of hemorrhage of 6.19% compared to patients presenting without hemorrhage of 0.33%. With increasing use of MR imaging, the percentage of cavernous malformations found incidentally approaches 40%.<sup>1</sup> Because the risk of hemorrhage is low in patients with CMs found incidentally, surgical or radiosurgery management may not be indicated. In contrast, patients presenting with symptoms of hemorrhage should be considered for therapeutic intervention due to a high risk for subsequent hemorrhage.

One option for the management of cavernous malformations is surgical intervention by CM resection. There is conflicting evidence in the literature regarding the effectiveness of CM resection, likely due to different methodologies used for determining efficacy. When post-operative outcomes are compared to pre-operative values, significant improvement is observed as demonstrated by improvements in the modified Rankin scale and decreased annual hemorrhage rate.<sup>5,6</sup> However, the results are limited by the fact that studies did not include a control group of patients that did not receive surgery. A recent retrospective study by Moultrie and colleagues compared the outcome of patients treated with surgical to conservative management. Patients who underwent CM resection had worsened short-term disability scores, increased risk of developing intracranial hemorrhage, and new focal neurologic deficits.<sup>7</sup>

While these results question the utility of surgical resection for management of cavernous malformations, there are situations in which CM resection may be beneficial. CM resection may be indicated in patients experiencing significant symptoms secondary to a cavernous malformation. For example, surgical resection has been found to significantly decrease seizures in CM patients presenting with epileptic seizures.<sup>8,9</sup> Similarly, patients with cavernous malformations in the brainstem experiencing significant symptoms (cranial nerve deficits, headaches, ataxia) have significant relief of their symptoms from minimally invasive resection, provided the CM can be accessed with minimal tissue perturbation.<sup>10</sup> Overall, it is clear that there are limitations to surgical treatment of cavernous malformations. Surgical resection should be reserved for easily accessible cavernous malformations in patients experiencing significant symptoms. For deeper-seated

malformations, alternative treatment such as radiosurgery should be explored.

Stereotactic radiosurgery is an appealing alternative to surgical resection because it is minimally invasive and lacks immediate morbidity.<sup>11</sup> Radiosurgery is believed to induce a hyalinization and thickening of blood vessels resulting in luminal closure, or a thrombotic process in which shunting can no longer occur.<sup>13,14</sup> In contrast to surgical resection, resolution of the cavernous malformation can take up to two years. Radiosurgery is generally reserved for treating cavernous malformations which are in eloquent and difficult to reach locations considered high risk for microsurgery. Approximately 20% of cerebral cavernous malformations are located in the brainstem region, demonstrating the need for minimally or non-invasive therapy.<sup>6</sup> In spite of its appeal, conservative management is still recommended until the cavernous malformation has bled twice, or is at significant risk for bleeding.<sup>12</sup>

Evidence suggests that patients with a high risk of hemorrhage would benefit most from stereotactic radiosurgery. Nagy et al. determined the annual hemorrhage rate for a single symptomatic, or asymptomatic bleed to be 2.4% before radiosurgical treatment, 5.1% in the two years after treatment, and 1.3% beyond two years. These findings suggest that in patients with asymptomatic CM, the risk of morbidity is different whether looking at short or long-term follow-up. Compared to conservative management, patients have a higher risk of morbidity the first two years after radiosurgical treatment. However, after two years the risk of morbidity is significantly decreased. In contrast, the risk for additional bleeds may be as high as 40% for patients that have had one previous symptomatic bleed.<sup>11</sup> Radiosurgery is considered to be effective for high risk CM patients. Nagy et al. found that the rebleeding rate went from 30.5% before treatment to 15% in the first two years and further fell to 2.4%

beyond two years.<sup>11</sup> Evidence in support of radiosurgery for high risk symptomatic patients is compelling, yet there is not a significant body of evidence supporting radiosurgery for incidental CMs.

The lack of randomized controlled studies, and a paucity of long term effects and safety data has limited the quality of evidence relating to radiosurgery, and so its indications and effectiveness are still debated.<sup>2</sup> Consequently, although SRS may be beneficial for surgically inaccessible CMs with a high risk for rebleed, it is rarely used. Patients who do not have a history of more than one significant bleed should undergo conservative management rather than SRS because of the significant risk of post-SRS bleeding for up to two years.<sup>13</sup>

Dose of radiation is also an important consideration when determining whether or not to use radiosurgery. In attempt to reduce the radiation-related sequelae in eloquent locations, some surgeons have reduced the dose of radiation used to treat cavernous malformations.<sup>11</sup> A significant concern with the reduction in radiation dose is whether or not the radiosurgery is effective at a lower dose. Current imaging studies are unable to demonstrate whether or not radiosurgery is effective, and consequently all studies are based on clinical outcomes.<sup>12</sup> Many studies have examined the safest, and most effective mean tumor margin dose for proper obliteration of the CM and determined it to be between 12 and 16 Gy.<sup>15</sup> Lunsford et al. found that their mean marginal dose of 16 Gy resulted in adverse radiation effects in 11.65% of their radiosurgically treated patients, and Pollock et al. reported adverse radiation effects in 59% of patients with a mean marginal dose of 18 Gy.<sup>13,16</sup> These studies highlight the significance of adverse effects that can occur with radiosurgery, and make the decision to treat a radiosurgically eligible incidental cavernous malformation more difficult, especially taking into consideration the eloquent areas involved.

Seong-Hyun Park and Chalouhi both suggest that radiosurgery is an alternative to microsurgery for treating patients with CMs in high-risk areas who are symptomatic and at risk for future bleeds.<sup>15,17</sup> The decision for radiosurgical intervention in asymptomatic patients with incidental cavernous malformations is a complex issue. Cavernous malformations have variable courses. Some may remain relatively benign, but others may bleed and cause significant neurological deficit. Current guidelines suggest that asymptomatic CM patients should be followed with serial imaging studies and periodic clinical exams to continually assess whether or not intervention is warranted.<sup>12</sup>

Additional research is needed to fully understand the utility of radiosurgery for treating cavernous malformations. Patients with high-risk or symptomatic cavernous malformations appear to benefit most from radiosurgery. The role of radiosurgery in treating incidentally found cavernous malformations is less clear. A randomized controlled trial comparing radiosurgery to conservative management would be most beneficial.

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