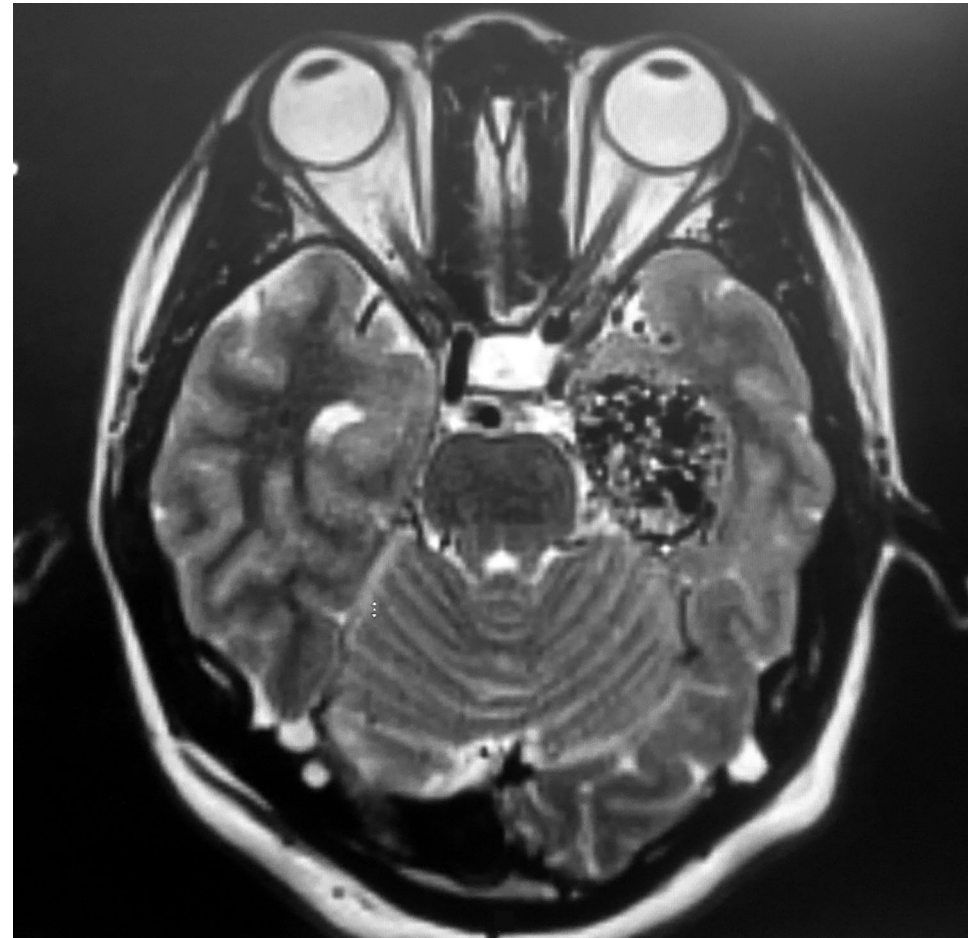




# Leksell Gamma Knife<sup>®</sup> Stereotactic Radiosurgery for the treatment of intracranial arteriovenous malformations (AVMs)



## Introduction

An intracranial arteriovenous malformation (AVM) is a high-flow vascular lesion in the brain, characterized by abnormal arteriovenous shunting through a tangled nidus of blood vessels, bypassing the normal capillary system<sup>1,2,3</sup>. Found in adult and pediatric populations, brain AVMs have an estimated incidence of 1.12-1.42 per 100,000<sup>4</sup> and a prevalence of around 18 per 100,000<sup>5</sup>. Ruptured AVMs carry a 30-50% risk of morbidity and a 10-20% risk of mortality<sup>6</sup>.

Although often asymptomatic<sup>7</sup>, brain AVMs can cause spontaneous intracranial hemorrhage in adults and children<sup>8</sup>. This is the first presenting symptom in 36-68% of cases<sup>9</sup> and can result in significant morbidity or death<sup>10</sup>. In addition to intracranial hemorrhage<sup>11</sup>, brain AVMs may cause headaches, epilepsy, and focal neurological impairment<sup>12</sup>.

Left untreated, the reported overall annual risk of hemorrhage due to a brain AVM ranges from 1-5%<sup>13</sup>, with risk increasing (1-7.5%)<sup>14</sup> following an initial AVM rupture<sup>15</sup>. The reported annual risk of hemorrhage for an unruptured AVM is between 1-4%<sup>16</sup>. Patients with a previous AVM rupture, a deep-seated lesion or high-grade AVM (characterized by large nidus volume, deep location and venous drainage) tend to experience higher rates of bleeding<sup>17</sup>. The annual risk of hemorrhage for such patients could be as high as 35%<sup>18</sup>.

A dural arteriovenous fistula (DAVF) is a rare type of intracranial AVM (comprising between 5-20% of all intracranial vascular malformations<sup>19</sup>) that occurs in the dura mater of the brain<sup>20</sup>, most frequently near the transverse, sigmoid and cavernous sinuses(CS)<sup>21</sup>. They can occur with or without cortical venous drainage (CVD)<sup>22</sup>. CS DAVFs and those without CVD are considered to have a more benign natural history but may present with ophthalmic symptoms, cranial nerve palsy or pulsatile tinnitus<sup>23</sup>.

Non-CS DAVFs and those with CVD often present with more severe symptoms, such as intracranial hemorrhage, seizures or focal neurological impairment<sup>24</sup>. CS DAVFs and those without CVD carry a lower risk of hemorrhage (0-1%)<sup>25</sup>, whereas the annual risk of hemorrhage for DAVFs with CVD is much higher, ranging from 6-19%<sup>26</sup>.

## Treatment options for AVMs

The neurological morbidity and mortality caused by a ruptured brain AVM, as well as the lifetime cumulative risk of hemorrhage for patients diagnosed at a young age<sup>27,28</sup>, is thought to warrant intervention. For unruptured AVMs, the potential benefit of treatment should be weighed against the lower risk of hemorrhage<sup>29</sup>.

Effective treatment options for AVMs, including DAVFs<sup>30</sup>, include microsurgical resection, endovascular embolization and stereotactic radiosurgery (SRS), or a combination of these approaches<sup>31</sup>. Medical observation is also an option for unruptured AVMs<sup>32</sup>. The most appropriate management for individual lesions and patients is decided by a multidisciplinary team<sup>33</sup>. The goal of treatment for brain AVMs is to reduce or eliminate symptoms and the annual risk of intracranial hemorrhage<sup>34</sup>.

Surgical resection immediately addresses an AVM rupture<sup>35</sup> and is often used as a first-line treatment for superficial lesions<sup>36</sup> and carefully selected patients<sup>37</sup>. However, this method can be highly invasive and is associated with increased risk for deep-seated and high-grade AVMs<sup>38,39</sup>.

Endovascular embolization is commonly used to treat DAVFs<sup>40</sup> or as an adjunctive method for the treatment of some AVMs<sup>41</sup>, achieving obliteration rates of 70–90% for DAVFs<sup>42</sup>, but only 5–40% for AVMs as a stand-alone treatment<sup>38</sup>. As with resection, this method is also associated with higher risks of morbidity and mortality for deep seated lesions and AVMs in eloquent regions of the brain<sup>43</sup>.

## SRS for the treatment of AVMs

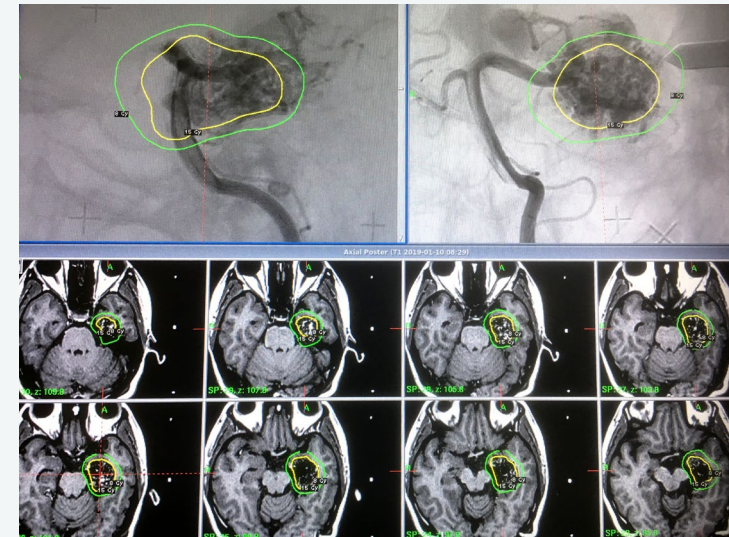
SRS is an important<sup>44</sup> and well-established method for treating brain AVMs<sup>45</sup> in appropriately selected adult or pediatric patients<sup>46</sup>. It is recommended by the International Stereotactic Radiosurgery Society (ISRS) as a safe and effective alternative to microsurgery for the treatment<sup>47</sup> of Spetzler-Martin Grade grade I–II AVMs and may be considered as a front-line treatment for such lesions<sup>35</sup>. In a separate report, ISRS Guidelines also state that SRS is safe and effective for many Spetzler-Martin grade III–V AVMs and should be considered as a front-line management strategy for such high-grade lesions alongside observation and microsurgery<sup>48</sup>. These guidelines further recommend that SRS may be the preferred option for high-grade lesions deemed less favorable for resection or following incomplete resection<sup>48</sup>.

As a non-invasive technique, SRS has particular value for AVMs in deep, inaccessible or eloquent regions of the brain<sup>49</sup>, for DAVFs where obliteration is not likely to be achieved using surgical approaches or embolization alone<sup>50</sup>, and for patients who are not eligible<sup>51</sup> or are unwilling to undergo surgery<sup>52</sup>. It has also been used as a salvage treatment following incomplete surgical resection of AVMs<sup>53</sup>, as a treatment option for patients with multiple AVMs<sup>54</sup>, for example due to hemorrhagic telangiectasia (HTT)<sup>55</sup>, and for trigeminal neuralgia-associated AVMs<sup>56,57</sup>.

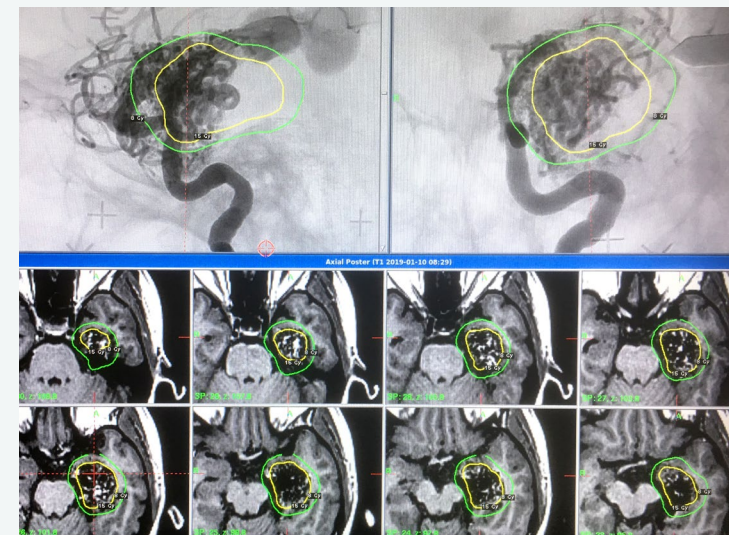
With SRS there is a latency period between irradiation and complete obliteration, during which time the risk of hemorrhage usually remains at baseline or lower<sup>58,42</sup>. Overall, SRS is reported to achieve complete AVM obliteration in 60–95%<sup>59</sup> of adult and pediatric patients, usually within three to five years of treatment<sup>60</sup>, and demonstrates low treatment-related toxicity rates<sup>61</sup>. Obliteration rates of 72% have been observed for grade III AVMs<sup>48</sup>, with lower rates (46% overall) reported for grade IV–V AVMs<sup>62,48</sup>. High-grade AVMs are associated with increased risk of radiation induced complications (RICs), which can be addressed by limiting the volume of healthy brain receiving 12 Gy (V12) and by considering techniques such as volume-staged SRS (VS-SRS) for larger lesions, as discussed below<sup>48</sup>.

For AVMs that are not completely obliterated three to five years after an initial SRS treatment, repeat SRS can be considered<sup>63</sup> as a salvage approach and has achieved good obliteration rates (51–77%) of residual AVMs in adult and pediatric patients<sup>64</sup>, with low risk of hemorrhage and radiation induced changes<sup>65</sup>. This strategy is recommended by the ISRS after a period of three to five years, especially when there is no further volumetric regression of the residual AVM<sup>66</sup>. Even a third repeat SRS treatment is considered a safe and effective management option for residual AVMs, when required<sup>67</sup>. For grade IV–V AVMs, the ISRS recommends consideration of repeat single-fraction SRS, volume-staged SRS or dose-staged SRS<sup>66</sup>.

SRS has also been shown to provide similar high overall obliteration rates (70–78% within three to four years)<sup>68</sup> and low complication rates for DAVFs<sup>69</sup>, either alone or in conjunction with embolization<sup>70</sup>. It is increasingly considered as an alternative to microsurgery or embolization for the treatment of this type of vascular malformation<sup>71</sup> and has achieved obliteration rates as high as 94% in symptomatic CS DAVFs<sup>72</sup>. The ISRS recommends SRS as a safe and effective treatment option for: patients with complex DAVFs<sup>42</sup> that are at high risk of not achieving complete obliteration with embolization alone; patients with refractory symptoms following previous embolization without complete DAVF obliteration; and patients with high-risk non-CS DAVFs or symptomatic CS DAVFs who are not candidates for, or have refused, embolization or microsurgery<sup>42</sup>.



**Vertebral contribution**



**Carotid contribution**

## **Gamma Knife Stereotactic Radiosurgery for the treatment of AVMs**

Gamma Knife SRS (GKSRS) is designed and dedicated for the treatment of intracranial lesions, and has been used to treat AVMs since the early 1970s<sup>73</sup>. Offering excellent localization accuracy, high conformity and steep dose gradients, GKSRS helps to ensure lower dose to healthy brain and better sparing of critical structures compared to other brain SRS techniques<sup>74</sup>. The safety and efficacy of GKSRS for the treatment of AVMs (including DAVFs) is well documented<sup>75</sup>. Studies also suggest that GKSRS is an effective option for larger lesions<sup>76</sup> and for AVMs in deep and/or eloquent regions of the brain<sup>77,78</sup>.

## **SRS for large, complex and high-grade AVMs**

SRS treatment of large (>10 cm<sup>3</sup>) and complex AVMs is challenging<sup>11</sup>. A reduced single-session dose designed to prevent toxicity in adjacent brain tissue may result in lower rates of complete nidus obliteration<sup>11</sup>. However, the use of conventional therapeutic doses may increase the risk of adverse radiation effects for large and complex AVMs treated with SRS<sup>79</sup>. Such challenges have been addressed in a number of ways:

### **SRS combined with embolization**

SRS combined with endovascular embolization has been used to treat selected patients with large and complex AVMs<sup>80</sup>, achieving obliteration rates as high as 86.4% after four years<sup>81</sup>. The aim of neoadjuvant embolization in this context is to reduce nidus volume prior to SRS<sup>82</sup>, lower the risk of hemorrhage<sup>83</sup>, and improve treatment outcomes<sup>84</sup>. However, one group reported no benefit to AVM obliteration rates with pre-SRS embolization compared to SRS alone in pediatric patients<sup>85</sup>. Another study proposes that adjuvant embolization after SRS may be beneficial for the treatment of AVMs with highly complex angioarchitecture that are at risk of hemorrhage during the latency period<sup>86</sup>.

Combined embolization and SRS has also been used for the treatment of complex DAVFs, where it is thought that embolization may provide partial protection from hemorrhage during the SRS latency period<sup>87</sup>.

### **Volume-staged SRS**

Volume-staged SRS has been shown to be an effective treatment option for large AVMs<sup>88</sup>. With this approach, a suitable large AVM nidus is carefully divided into multiple target volumes, which are treated in consecutive sessions three to six months apart<sup>89</sup>. This helps to ensure adequate dose to the target while reducing radiation to normal brain<sup>48</sup>, resulting in improved obliteration rates and reduced RICs for large volume AVMs<sup>90,91</sup> without increasing risk of hemorrhage during the latency period. Radiation overlap should be avoided within normal brain tissue and smaller volumes per stage are advised with this approach for deep AVMs<sup>11</sup>.

### **Hypofractionated SRS**

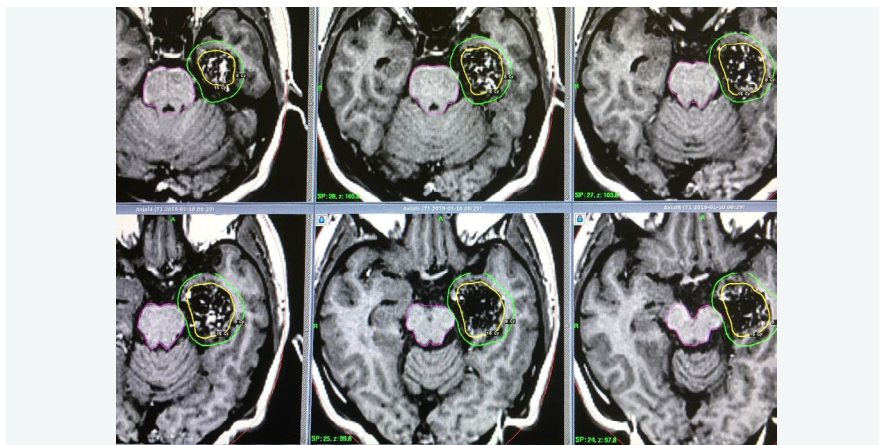
Hypofractionated SRS has been described for the treatment of AVMs that are challenging due to their size or location<sup>92</sup>, yielding obliteration rates of between 62–88%<sup>92</sup> with an acceptable safety profile<sup>92</sup>. This approach involves the delivery of multiple (two to five) smaller doses of radiation to the entire AVM over several weeks, thereby delivering a higher overall dose to the target while protecting normal and eloquent regions of the brain<sup>92</sup>.

### **Time-staged SRS**

Time-staged SRS, defined as 'intentional repeat SRS targeting the entire nidus at three-year intervals', is reported to produce favorable long-term outcomes and complication rates in the treatment of large AVMs (up to 30 mL)<sup>93</sup>.

## SRS targeting and dose

SRS targets the entire AVM nidus, excluding the draining veins from the target volume<sup>94</sup>. The AVM/DAVF targets and their angioarchitecture are precisely defined for SRS planning using a variety of imaging techniques (alone or in combination), such as digital subtraction angiography (DSA), thin-slice (one to two mm) magnetic resonance imaging (MRI) (e.g. T1W, T2W, contrast-enhanced volumetric, multiplanar reformation, fast spin echo, Time of Flight), computed tomography (CT), CT angiography, triple magnetic resonance angiography (triple-MRA:4D ASL, contrast-enhanced Time-Resolved, post contrast Time of Flight)<sup>95</sup>, rotational angiography (RA), biplanar angiography and Diffusion Tensor Imaging (DTI)<sup>96</sup>.



### Dose plan

Serial MRI or MRA is generally used for routine post-SRS imaging (for example, time-averaged 3D flow MRI<sup>97</sup> or MR perfusion imaging), with AVM or DAVF obliteration confirmed by DSA or MRA<sup>98</sup>.

Reported median marginal doses that have been used to treat AVMs and DAVFs range from 15 to 25 Gy<sup>99</sup>, usually delivered along a 50% isodose line<sup>100</sup>, depending on factors such as the age of the patient, the size of the nidus, and its proximity to critical structures in the brain<sup>101</sup>.

It has been suggested that higher marginal doses (e.g. 18–25 Gy)<sup>102</sup> may be optimal for obliteration<sup>103</sup> and nonhemorrhagic outcomes, with lower doses reserved for cases where higher doses are intolerable<sup>104,105</sup>. Dose reduction may not be required for repeat SRS<sup>106</sup>, with the ISRS suggesting that the optimal dose for repeat single-fraction SRS is within the range of 16–20 Gy<sup>43</sup>. The minimal margin dose per stage recommended for volume-staged SRS is 17 Gy, depending on the location of the AVM<sup>107</sup>.

For grade I–II AVMs, the ISRS estimates that the probability of complete obliteration following SRS is 65–70% at 15 Gy, 75–80% at 18 Gy and 85–90% at 20–25 Gy<sup>108</sup>.

Previous AVM hemorrhage, higher margin doses, non-eloquent locations, lower grade, low-moderate flow, compact lesions and smaller AVM volume have all been suggested as predictive factors for complete AVM obliteration<sup>109</sup>. Additionally, peripheral location is thought to be associated with lower post-SRS hemorrhage rates<sup>104</sup>.

## Treatment toxicity

SRS is considered a safe treatment for AVMs and DAVFs, with all or most (>97%) patients having their neurological status preserved<sup>110</sup>. Early radiologic complications, if they occur, are usually asymptomatic and self-resolving<sup>111</sup>. Symptomatic radiation-induced changes (RICs) are reported to occur in 7–9% of cases overall, 0–5.3% of which are permanent<sup>112</sup>. Delayed cyst formation, expanding hematoma, and radiation-induced tumors are rare, occurring in only 0.6–2.4%, 0–0.28% and 0–0.24% of cases respectively<sup>113</sup>.

Larger AVMs and those with neoangiogenesis are associated with more severe RICs<sup>114</sup>. The ISRS and other investigators state that minimization of RIC risk is associated with a reduced total brain/non-AVM volume receiving 12 Gy<sup>115</sup>.

A number of medical therapies may be considered for the management of symptomatic RICs, including corticosteroids, vitamin E, pentoxifylline, hyperbaric oxygen, and bevacizumab<sup>43</sup>.

## Conclusions

SRS is considered safe and effective for the treatment of brain AVMs, including DAVFs, in both adult and pediatric patients<sup>116</sup>. It is increasingly used as a stand-alone, first line treatment option for selected patients, particularly for low grade AVMs and for patients who are not eligible or are unwilling to undergo endovascular or surgical approaches<sup>117</sup>, and is associated with minimal risks of hemorrhage and low rates of RICs in appropriately selected patients<sup>118</sup>.

SRS is a non-invasive treatment option, offering minimal side effects, faster recovery, and improved comfort compared to more invasive techniques. With innovative Gamma Knife technology, patients can receive imaging and treatment on the same day in a convenient outpatient setting.

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