Long-term complications after gamma knife surgery for arteriovenous malformations

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Object. The authors analyzed the long-term complications that occur 2 or more years after gamma knife surgery (GKS) for intracranial arteriovenous malformations (AVMs).

Methods. Patients with previously untreated intracranial AVMs that were managed by GKS and followed for at least 2 years after treatment were selected for analysis (237 cases). Complete AVM obliteration was attained in 130 cases (54.9%), and incomplete obliteration in 107 cases (45.1%). Long-term complications were observed in 22 patients (9.3%). These complications included hemorrhage (eight cases), delayed cyst formation (eight cases), increase of seizure frequency (four cases), and middle cerebral artery stenosis and increased white matter signal intensity on T2-weighted magnetic resonance imaging (one case of each). The long-term complications were associated with larger nidus volume (p < 0.001) and a lobar location of the AVM (p < 0.01). Delayed hemorrhage was associated only with incomplete obliteration of the nidus (p < 0.05). Partial obliteration conveyed no benefit. Delayed cyst formation was associated with a higher maximal GKS dose (p < 0.001), larger nidus volume (p < 0.001), complete nidus obliteration (p < 0.01), and a lobar location of the AVM (p < 0.05).

Conclusions. Incomplete obliteration of the nidus is the most important factor associated with delayed hemorrhagic complications. Partial obliteration does not seem to reduce the risk of hemorrhage. Complete obliteration can be complicated by delayed cyst formation, especially if high maximal treatment doses have been administered.

Key Words • gamma knife surgery • arteriovenous malformation • complication • cyst • hemorrhage

Thirty years after the initial report by the Leksell group9 GKS has become a standard procedure for the treatment of selected patients with intracranial AVMs. The combination of high efficacy and minimal invasiveness makes this modality especially attractive for lesions located in or adjacent to eloquent brain structures, which are considered not amenable to safe resection;14 however, GKS for AVMs is not a completely risk-free procedure and may be accompanied by several well-known complications. The latter has a wide spectrum and temporal distribution but may be separated into two main groups. First there are complications that occur within 2 years of treatment before and during the development of the radiation-induced vascular changes to the target lesion. Second there are those which occur thereafter.6 Although the former are widely reported in the neurosurgical literature13,14 the types and risk factors for the latter, which also include cases of treatment failure are less well documented.10 The objective of the present study was investigation of the long-term complications after GKS for intracranial AVM.

Abbreviations used in this paper: AVM = arteriovenous malformation; CT = computerized tomography; GKS = gamma knife surgery; MR = magnetic resonance.
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Comparison of clinical, radiosurgical, and follow-up variables in the whole cohort of patients who were treated by GKS for intracranial AVMs and followed more than 2 years after treatment and the subgroup of those who exhibited long-term complications

<table>
<thead>
<tr>
<th>Variable</th>
<th>All 237 Patients (%)</th>
<th>Subgroup w/ Long-Term Complications (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean age ± SD (yrs)</td>
<td>30.1 ± 4.2</td>
<td>30.4 ± 13.7</td>
</tr>
<tr>
<td>male/female</td>
<td>144/93</td>
<td>13.9</td>
</tr>
<tr>
<td>hemorrhage</td>
<td>130 (54.9)</td>
<td>8 (36.4)</td>
</tr>
<tr>
<td>nonhemorrhage</td>
<td>107 (45.1)</td>
<td>14 (63.6)</td>
</tr>
<tr>
<td>lobar</td>
<td>159 (67.0)</td>
<td>21 (95.5)</td>
</tr>
<tr>
<td>nonlobar</td>
<td>78 (33.0)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>mean nidus vol ± SD (ml)</td>
<td>4.7 ± 1.9</td>
<td>7.6 ± 5.4§</td>
</tr>
<tr>
<td>Spetzler–Martin grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I &amp; II</td>
<td>102 (43.0)</td>
<td>9 (40.9)</td>
</tr>
<tr>
<td>III &amp; IV</td>
<td>135 (57.0)</td>
<td>13 (59.1)</td>
</tr>
<tr>
<td>mean max dose ± SD (Gy)</td>
<td>42.8 ± 6.4</td>
<td>45.6 ± 10.4</td>
</tr>
<tr>
<td>mean margin dose ± SD (Gy)</td>
<td>20.2 ± 3.1</td>
<td>20.7 ± 3.7</td>
</tr>
<tr>
<td>complete obliteration</td>
<td>130 (54.9)</td>
<td>15 (68.2)</td>
</tr>
<tr>
<td>incomplete obliteration</td>
<td>107 (45.1)</td>
<td>7 (31.8)</td>
</tr>
<tr>
<td>mean follow up ± SD (yrs)</td>
<td>6.8 ± 1.1</td>
<td>5.5 ± 2.5§</td>
</tr>
</tbody>
</table>

* SD = standard deviation.
† p < 0.05.
‡ p < 0.01.
§ p < 0.001.

All patients were treated with the Leksell Gamma Knife model B (Elekta Instrument AB Stockholm, Sweden). The treatment planning was performed using KULA or Leksell GammaPlan (Elekta Instrument) based on the combination of the angiographic data, contrast-enhanced CT images, and later thin-sliced MR images. All patients included in the present series were treated before initiation of the staged-volume concept for treatment of large AVMs; therefore complete coverage of the nidus by the prescription isodose line (40–80%) by using single or multiple isocenters was performed in each case. The choice of the radiation dose depended on the target volume. The mean maximum dose was 42.8 ± 6.4 Gy (range 24–60 Gy). The mean margin dose was 20.2 ± 3.1 Gy (range 12–26 Gy).

The majority of patients were followed after treatment by clinical examination at least once every 6 months for 3 years and once per year thereafter. Control cerebral angiography was performed at least 1 year after GKS if complete obliteration of the nidus was not attained. Angiography was repeated 2 and if necessary 3 years after treatment. Additional angiography was not performed thereafter unless further management of the AVM was planned. Examinations by using CT and/or MR imaging were performed at least yearly. The mean follow-up time was 6.8 ± 1.1 years (range 2–12.5 years).

Statistical Analysis

The two-tailed t-test and chi-square test were conducted for statistical analysis as appropriate. The level of statistical significance was determined at p < 0.05.

Results

Obliteration Rate

Complete obliteration of the nidus was identified by angiography in 130 (54.9%), partial obliteration (>50% reduction of the nidus volume) in 60 (25.3%), and less than 50% reduction of the nidus volume or absence of obliteration in 47 (19.8%) cases.

Morbidity Rate

Long-term complications after GKS were observed in 22 (9.3%) patients. These included eight (3.4%) hemorrhages, three (13.5%) of which were fatal. There were eight (3.4%) delayed cyst formations, four (1.7%) increases in seizure frequency, a nonsymptomatic increase of white matter signal intensity on T2-weighted MR imaging in one patient (0.4%), and an asymptomatic middle cerebral artery stenosis in one patient (0.4%). The mean annual incidence of long-term complications was 1.4%. Hemorrhage was observed a mean latency after GKS of 4.3 ± 2.7 years (range 2–9 years). Cyst formation was observed a mean latency after GKS of 6.8 ± 1.6 years (range 5–9 years). This difference reached statistical significance (p < 0.05).

Factors Associated With Long-Term Complications. The frequency of long-term complications was associated with larger nidus volume (p < 0.001) and lobar location of AVM (p < 0.01) (Table 1).

Delayed hemorrhage as illustrated in Fig. 1 was associated only with incomplete obliteration of the nidus (p < 0.05). Three of the 60 patients with partially obliterated AVMs suffered a hemorrhage. Four patients with unchanged lesions had a hemorrhage. The frequency of the complication is not significantly different in the two groups.

Delayed cyst formation as illustrated in Fig. 2 was associated with a larger nidus volume (p < 0.001), higher maximal dose (p < 0.001), complete obliteration of the nidus (p < 0.01), and a lobar location of the lesion (p < 0.05).

Mortality Rate

As noted previously during the follow-up period three
patients died of intracerebral hemorrhage from the residual nidus. The disease-related mortality rate during a long-term follow up of 2 or more years after GKS for intracranial AVM was 1.3%.

Discussion

Radiosurgery, particularly GKS, has become a standard modality for the treatment of selected patients with intracranial AVM. Its clinical effectiveness results from radiation-induced obliteration of pathological vessels by a variety of mechanisms.10 These changes are gradual and need time for their completion. The obliteration of AVMs is preceded by a latency period which lasts approximately 2 years but may be shortened if the treatment dose is increased.6 Various complications may occur during this time and these are well documented with particular emphasis directed to the continued risk of hemorrhage until the lesion has been obliterated.18 This complication is encountered with an average annual incidence of 1.8 to 4% during the first 2 years after treatment.46 The complication may occur within the first 6 months after treatment in 45% of cases.6 Factors that predispose to hemorrhage during the latency period included advanced patient age, large AVM volume, and a low margin treatment dose.6

Hemorrhagic complications occurring after completion of the latency period have not received significant attention in the neurosurgical literature.11 Karlsson, et al.,6 observed 44 hemorrhages in 1593 patients (2.8%) that occurred 2 or more years after GKS for AVM. Seventeen of these occurred more than 5 years after treatment and eight occurred more than 10 years after GKS. In the series by Yamamoto, et al.,11 the incidence of this complication was 3.8%. On the long-term follow up in the present series the frequency of hemorrhage in patients with AVM treated by GKS was 3.4%, and 37.5% of these were fatal. The presence of hemorrhagic complications was associated with only one factor, namely incomplete obliteration of the nidus. It should be noted that in the present series partial obliteration did not show any efficacy in prevention of hemorrhagic complications during the long-term follow up.

It should also be noted that complete angiographic occlusion of an AVM may not guarantee freedom from risk of delayed hemorrhage. Two such cases have been reported previously,10,11 and one was observed in the present series. Recanalization of thrombi and the development of an abundant capillary network in the granulation tissue are thought to be the cause of bleeding.10 Moreover the quality of the images may also play a part in this complication. Abnormal contrast enhancement in the target region after successful GKS for AVM can be observed in 60% of patients.7

The overall obliteration rate in the present series was 54.9%, which is lower than that usually reported (60.4–81.3%).1,2,4,5,11 This may be related to case selection with inclusion of only previously untreated patients who did not obtain any other treatment the first 2 years after GKS. In addition this series contained a relatively high percentage of patients with high-grade AVMs, the larger size of which enforce a low prescription dose. Target error is also known to be a possible cause of treatment failure.1,2,4,5 It may be noted that 25.3% of cases in which partial obliteration was attained may well go on to complete obliteration at a later...
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date. Complete obliteration of AVMs up to 60 months after GKS had been reported.1

In each case in the present series the treatment planning was performed with the intention of achieving complete coverage of the nidus by the prescription isodose. Treatment doses were reduced in cases of large lesions. Probably the higher rate of AVM obliteration could be attained if higher treatment doses were used.4,6 The main pitfall of the high-dose GKS is the radiation-induced injury to the surrounding brain tissue especially if the target volume is large.4,5 Recently the concept of staged radiosurgery for treatment of large AVMs had been proposed1,4 and is now in use in our clinic. The success rate of this technique and its place in the management of AVMs awaits determination. Colombo, et al.,1 reported two cases of radiation necrosis and a high incidence of hemorrhage in patients treated with partial volume irradiation. Radiation necrosis has been reported with a frequency 1.7 to 7.6% after GKS for AVMs.1,3,11 It was not observed in any case in the present series.

Higher maximal treatment dose, a larger nidus volume, a lobar location of the AVM, and its complete obliteration were associated with delayed cyst formation, which was observed in the present series with an incidence of 3.4% at nearly 7 years after treatment. There are some large series with adequate follow up in which this complication was not observed at all;1 however, it has been reported with a frequency of 7.9 to 28% in others.2,11 The origin of this complication remains speculative at the present time.

Although hemorrhage and delayed cyst formation represent the most frequent and, probably, the most clinically important long-term complications after GKS for intracranial AVMs, other less common conditions can be seen during long-term follow up. In four patients in the present series (1.7%) there was an increase in the frequency of pre-existing seizures, which was noted several years after treatment. In a multicenter analysis Flickinger, et al.,3 found this complication in 22% of patients who exhibited neurological sequelae after radiosurgery for an AVM and attributed it to radiation injury of the brain parenchyma. The only radiation damage in the present series was an asymptomatic increase in the white matter signal intensity on T2-weighted MR imaging in a single case. Thus radiation brain damage does not explain the observed increase in epilepsy frequency in this series. Kihlstrom, et al.,7 described the same complication in three of 18 asymptomatic patients with proven obliteration of the AVM. The mechanism remains speculative. Finally, one case of asymptomatic middle cerebral artery stenosis similar to a case reported by Yamamoto, et al.,11 was found in the present series. It is not clear whether it represents a consequence of treatment or resulted from intercurrent disease.

Conclusions

The risk of complications after GKS for intracranial AVM continues for as many as 10 years after treatment; thus careful long-term follow up of these patients is important. Partial obliteration of the nidus does not seem to reduce the risk of hemorrhagic complications. Complete obliteration can be complicated by delayed cyst formation especially if a higher maximum prescription dose was administered.

References


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