Radiation-induced change after Gamma Knife radiosurgery for cerebral arteriovenous malformations

Hak Su Lee, MD¹, Hae Yu Kim, MD, PhD¹,², Sun-Il Lee, MD, PhD¹,², Joon-Bum Woo, MD², Sung Chul Jin, MD, PhD², Moo Seong Kim, MD, PhD³

¹Gamma Knife Center, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea
²Department of Neurosurgery, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea
³Department of Neurosurgery, Busan Paik Hospital, Inje University College of Medicine, Busan, Korea

Objective: Radiation-induced change (RIC) on magnetic resonance imaging after Gamma Knife radiosurgery (GKRS) for cerebral arteriovenous malformations (AVMs) is not rare. We reviewed patients who underwent GKRS for AVMs and analyzed the results and factors associated with RIC.

Methods: We reviewed 189 patients who underwent GKRS for AVMs between October 2002 and August 2017. All patients were followed up for at least 3 years. This study included 111 males and 78 females (mean age, 39.63 years; range, 3–79 years). Nineteen patients underwent pre-GKRS embolization. Seventy-six patients had ruptured AVMs and 113 had unruptured AVMs. We analyzed obliteration and RIC occurrence rates. Several demographic and clinical factors were analyzed to determine the influence of AVM obliteration on RIC occurrence.

Results: The overall obliteration rate (OR) was 72.49% (137/189) at the final follow-up. The actuarial OR was 55.5% 36 months after GKRS. The overall RIC occurrence rate was 28.04% (53/189), and the actuarial RIC occurrence rate was 26.8% 24 months after GKRS. The OR showed a statistically significant difference according to AVM rupture (p<0.01) and sex (p<0.01). The RIC occurrence rate was significantly associated with AVM rupture (p<0.01), lesion volume (p=0.04), and treatment volume (p=0.03). Other factors showed statistically non-significant relationships.

Conclusion: The overall OR after GKRS for AVMs was comparable to the results of other previous reports. RIC is a common postoperative outcome following GKRS for AVMs. In this study, the OR was higher in ruptured AVMs and male patients, whereas RIC occurred more frequently in larger and unruptured AVMs.

KEY WORDS: Radiation, Radiosurgery, Arteriovenous malformations

INTRODUCTION

Arteriovenous malformations (AVMs) are intracranial vascular abnormalities that shunt blood from the arteries to veins, bypassing the capillary bed [1,2]. Gamma Knife radiosurgery (GKRS) is the standard treatment for AVMs wherein, total obliteration of AVMs was achieved during long-term follow-up [3-7]. How-
However, adverse effects, such as radiation-induced necrosis, edema, and cysts, may be observed during this period, radiation-induced changes (RIC), being the most common [4]. It can be observed 1 or 2 years postoperatively on magnetic resonance imaging (MRI) [7-10].

RICs are typically observed 6–18 months after radiosurgery and are mostly asymptomatic [2,8,10-14]. The severity of RICs and the associated clinical manifestations can vary from small or minimal asymptomatic signals to massive brain swelling with increased intracranial pressure and occasionally, leading to permanent neurological deficits. Most symptomatic RICs are transient and are managed medically. RICs show variations in occurrence rate, duration, and symptoms. In this study, we retrospectively reviewed patients who underwent GKRS for AVMs and investigated obliteration and RIC occurrence rates and assessed the associated factors.

MATERIALS AND METHODS

We reviewed 189 patients who underwent GKRS for AVMs between October 2002 and August 2017. Demographic data are shown in Table 1. The institutional review board approved the collection and review of patient data. And, this was a retrospective observational study that only required a review of previously collected patient data. Patient-identifying information was not revealed in this study, so informed consent from the patients was not required. All patients were followed up for at least 3 years. This study included 111 males and 78 females. The mean age of the patients was 39.63 years (range, 3–79 years). Nineteen patients underwent pre-GKRS embolization. Seventy-six patients had ruptured AVMs and 113 had unruptured AVMs. It was hypothesized that AVMs would be completely obliterated when confirmed by cerebral angiography in the absence of additional AVM nidus on MRI during follow-up after GKRS. RIC occurrence was defined as a high-signal change around the AVMs on T2 weighted and fluid-attenuated inversion recovery images. The imaging findings were double-checked by two different neurosurgeons. All medical records were reviewed to identify clinical symptoms at follow-up when RIC was detected for the first time. Fig. 1 showed an illustrative case showing RIC. Forty-five-year-old female underwent GKRS for unruptured AVM in left occipital subcortex. Lesion volume was 17.3 cm³ and maximum dose was 44 Gy. Fifty percent isodose line was set on AVM margin. One year later, routine follow-up MRI showed decreasing AVM

Table 1. Summary of demographic data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male:female)</td>
<td>111:78</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>39.63 ± 16.78</td>
</tr>
<tr>
<td>Ruptured:unruptured</td>
<td>76:113</td>
</tr>
<tr>
<td>Pre-GKRS embolization</td>
<td>19</td>
</tr>
<tr>
<td>Follow-up period (mo)</td>
<td>68.05 ± 23.05</td>
</tr>
<tr>
<td>Diameter of AVM (cm)</td>
<td>1.72 ± 1.15</td>
</tr>
<tr>
<td>Lesion volume (cm³)</td>
<td>7.23 ± 10.31</td>
</tr>
<tr>
<td>Treatment volume (cm³)</td>
<td>7.40 ± 10.48</td>
</tr>
<tr>
<td>Margin dose* (Gy)</td>
<td>17.40 ± 4.46</td>
</tr>
<tr>
<td>Maximum dose (Gy)</td>
<td>34.18 ± 9.33</td>
</tr>
</tbody>
</table>

Values are presented as number only or mean ± standard deviation. GKRS: Gamma Knife radiosurgery, AVM: arteriovenous malformation. *We set the margin dose as 50% of the maximum dose to treat the AVMs.

Fig. 1. (A) A 45-year-old female underwent Gamma Knife radiosurgery for an unruptured arteriovenous malformation (AVM) in the left occipital subcortex. (B) The lesion volume was 17.3 cm³ and the maximum dose was 44 Gy. The 50% isodose line was set on the AVM margin. (C) One year later, routine follow-up magnetic resonance imaging showed a decreasing AVM nidus. However, radiation-induced change was observed around the AVM nidus. Fortunately, the patient showed no clinical symptoms.

https://doi.org/10.52662/jksfn.2023.00031
RIC after GKS for cerebral AVM nidus. However, RIC was observed around the AVM nidus. Fortunately, the patient showed no clinical symptom.

We analyzed obliteration and RIC occurrence rates. Factors such as age, sex, AVM diameter, lesion volume, treatment volume, isodose, marginal dose, maximal dose, pre-GKRS embolization, and presence or absence of rupture were analyzed to determine the influence of obliteration rate (OR) and RIC occurrence rate.

Statistical analysis
MedCalc was used for the statistical analysis. Descriptive statistics for demographic and clinical variables were obtained. The total obliteration and RIC occurrence rates were estimated using survival analysis. The Cox proportional hazard model was used to evaluate the risk factors. Significance was determined using a two-tailed p-value of less than 0.05.

RESULTS
The overall OR for AVMs was 72.49% (137/189) at the final follow-up. The actuarial OR 36 months after GKRS was 53.5%. The OR showed statistically significant differences according to ruptured AVM or not (p < 0.01) (Fig. 2) and sex (p < 0.01) (Fig. 3). However, the OR was not related to age, AVM diameter, lesion volume, treatment volume, isodose, marginal dose, maximal dose, pre-GKRS embolization, rupture, lesion location, or RIC occurrence.

The overall RIC occurrence rate was 28.04% (53/189), and the actuarial RIC occurrence rate was 26.8% 24 months after GKRS (Fig. 4). The occurrence of unruptured AVM rate was higher in unruptured AVMs than in ruptured AVMs (p < 0.01) (Fig. 5), AVM volume (p = 0.04), and treatment volume (p = 0.03) (Table 2). Other factors were not related to RIC occurrence rate and statistically insignificant.

Most patients exhibited no clinical symptoms. When we recognized RIC on follow-up MRI, only 11 patients showed clinical symptoms. Seven patients complained of new-onset headache, two complained of dizziness, and two patients had temporary motor weakness that developed after GKRS. Fortunately, none of the patients exhibited any new neurological deficits.

DISCUSSION
RICs are common findings on follow-up brain images after GKRS; however, the mechanisms underlying their occurrence are not completely understood. Direct irradiation of glial cells, particularly oligodendrocytes, may lead to demyelination [8,15,16]. In animal studies, oligodendrocytes have been shown to play an important role in the demyelination of white matter [16]. In the present study, ruptured AVM were associated with a lower RIC occurrence rate after GKRS. We hypothesized that brain tissue

Fig. 2. The obliteration rate of ruptured arteriovenous malformations was higher than that of unruptured malformations (p<0.01).

Fig. 3. The obliteration rate in male patients was higher than that in female patients (p<0.01).
The overall radiation-induced change (RIC) occurrence rate was 28.04%, and the actuarial RIC occurrence rate was 26.8% at 24 months after Gamma Knife radiosurgery.

The incidence of radiation-induced change (RIC) in unruptured arteriovenous malformations was higher than that in ruptured malformations (p<0.01, r=0.39).

**Table 2.** Risk factors related to radiation-induced change occurrence

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>AVM diameter</td>
<td>1.28</td>
<td>0.99–1.66</td>
</tr>
<tr>
<td>Lesion volume</td>
<td>0.71</td>
<td>0.52–0.97</td>
</tr>
<tr>
<td>Treatment volume</td>
<td>1.43</td>
<td>1.05–1.94</td>
</tr>
<tr>
<td>Rupture of AVM</td>
<td>0.21</td>
<td>0.08–0.54</td>
</tr>
<tr>
<td>Isodose</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>Margin dose</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Maximal dose</td>
<td>0.87</td>
<td></td>
</tr>
</tbody>
</table>

AVM: arteriovenous malformation, HR: hazard ratio, CI: confidence interval.

* p-value<0.05.

damage caused by hemorrhage around AVMs could reduce the amount of tissue irradiated by GKRS. This could mean that less radiation damage to the glial cells around the AVMs evokes fewer RICs. Radiation energy from GKRS can cause endothelial cell damage and subsequent breakdown of the blood–brain barrier [17]. These changes provoke brain edema, which can be observed in RICs. Some authors have reported that radiation damage to lipid membranes can induce the production of free radicals, causing membrane dysfunction and cell death [18]. These changes can be represented by RICs. Lee et al. [19] reported that serum vascular endothelial growth factor and endostatin levels could affect RICs after GKRS for AVMs. Some authors have reported that vascular volume radiated by GKRS is a risk factor because RICs are more frequent in AVM patients than in tumor patients [11,20].

In this study, the risk factors for RICs are rupture, AVM volume, and treatment volume. Rupture of AVM is the most important risk factor. Previous hemorrhage is negative risk factor of RIC occurrence in our study. Kim et al. [21] reported about negative correlation of hemorrhage history of AVM and RIC occurrence. Many authors reported that no hemorrhage history is the risk factor of RIC occurrence [8,10,22,23]. Although hemosiderin is known to be sensitive to radiation, the clinical evidence is lack [8]. Most of the reviewed literatures suggested that perinidal gliosis
and fluid filled space after hemorrhage from AVM are protective mechanisms against the development of RIC. However, Flickinger et al. [20] reported that prior hemorrhage is not associated with reduction of RIC occurrence. Han et al. [24] reported negative correlation of hemorrhage history and RIC occurrence, but the statistics is not significant.

AVM volume is the other important risk factor [2,13,20,25]. This supports the idea that endothelial damage caused by radiation could be a mechanism underlying RIC occurrence. Larger AVMs contain more endothelial tissue, which can cause RIC more frequently. Some authors have reported that brain tissue changes caused by radiation are affected by the treatment volume, radiation dose, treatment fractions, and the interval between fractions [8,20]. Although we did not analyze the fraction of GKRS as a risk factor for RIC occurrence because of the limited number of fractionation cases, the radiation fraction could be a controversial factor for RICs. Yen et al. [8] showed that fractionated GKRS is not a risk factor for RIC. However, we believe that fractionation planning for AVMs can be applied to a large number of AVMs. Therefore, the fractionation factor is easily affected by the AVM volume factor. A large AVM volume is a risk factor for RIC. van den Berg et al. [26] reported that the occurrence of RIC could be related to the total obliteration of AVMs. In this study, the relationship between RIC occurrence and AVM obliteration was not statistically significant.

Majority of patients with RIC after GKRS present with minimal or no neurological symptoms, thereby complicating its diagnosis based on certain symptoms. Ilyas et al. [10] reported that symptomatic RIC was significantly associated with deep AVM location. We believe that radiation dose to deep AVMs which have a larger amount of surrounding tissue and a more compromised venous drainage system could be a significant risk factor for RIC incidence. RIC in the deep brain easily compresses the eloquent area, which provokes neurological symptoms.

Patients with RICs usually do not require treatment as they are asymptomatic. Fortunately, in this study, only two patients presented with new-onset neurological symptoms related to RICs, which subsided spontaneously with the traditional protocol of corticosteroid use. Moreover, surgical resection is advised in patients who do not respond successfully to corticosteroids [27]. Other new treatments such as bevacizumab, vitamin E, anticoagulants, and pentoxifylline could have been attempted in anecdotal cases [28-30].

CONCLUSION

The overall OR after GKRS for AVMs was comparable to the results of previous reports. RIC is a common finding following GKRS for AVMs. Fortunately, most patients with RIC do not present with neurological symptoms, thereby eliminating the need for significant management. In this study, the OR was higher in ruptured AVMs and male patients, and RIC occurred more frequently in larger and unruptured AVMs. The risk factors related to OR and RIC occurrence have been debated, and further investigation is needed to identify definite and helpful factors or biomarkers for GKRS in clinical settings.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES


https://doi.org/10.52662/jksfn.2023.00031
gamma knife radiosurgery: rate of obliteration and complications. Neurosurgery 2007;60:1005-14; discussion 1015-6