Long-Term Side Effects of Radiosurgery for Arteriovenous Malformations

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Abstract

In this report, our experiences with 181 consecutive patients who underwent Gamma Knife radiosurgery (GKRS) for arteriovenous malformations (AVMs) during an approximately quarter century period from 1978 to 2002 will be summarized along with much of what we have learned from a wealth of already published data. During the mean post-GKRS follow-up period of 10.2 years (range, 5.4–30.6), 15 (8.3%) of our 181 patients experienced stereotactic radiosurgery-related, symptomatic complications. Among these 15 patients, 12 manifested complications 5 years or more after GKRS. Furthermore, in 5 of these 12, the complications were seen 10 or more years after GKRS. In the present series, the actuarial complication rates computed using the Kaplan-Meier method were 2.3% at the fifth, 8.2% at the tenth, 15.2% at the fifteenth and 31.1% at the twentieth post-GKRS year. AVM volumes, Pollock-Flickinger AVM scores, the initial presentation of bleeding and centrally located AVMs were demonstrated to be significantly associated with the risk of delayed complications after GKRS (p < 0.05). There was a significant difference in complication rates between two patient groups, based on whether dose planning was performed using the older (Kula) or the modern (Gamma Plan) system (18.0 vs. 4.6%, χ² p = 0.0002). Although GKRS is undoubtedly an alternative to microsurgical resection for appropriately selected AVMs, we must weigh treatment results against complication risks which are not negligibly low.

With recent advances in both preoperative and intraoperative neuroimaging, as well as microsurgical instruments and techniques, neurosurgeons can resect many arteriovenous malformations (AVMs) completely with an acceptably low morbidity rate. Although this is unquestionably ideal, some AVMs cannot be resected safely even by the most experienced neurosurgeon because they are located within or near a critical brain structure or because the patient has contraindications for general anesthesia. The role of embolization as radical treatment is considered to be relatively limited in the management of AVM patients because only 10–20% of AVMs are completely curable using this technique alone [1, 2]. Instead, embolization is widely used as a presurgical or preradiosurgical procedure to reduce both nidus size and blood flow [3]. In contrast, stereotactic radiosurgery (SRS) is widely accepted as an alternative
to microsurgery in the treatment of relatively small AVMs, particularly in deep brain locations (i.e. brainstem, basal ganglia or thalamus) or critical lobar areas (i.e. sensorimotor, speech or visual cortex) [4–18]. Since the historical reports by Steiner et al. [17] followed by those of Lunsford et al. [11], Colombo et al. [5, 6] and Friedman and Bova [7] as well as ours [19], complication rates after SRS for AVMs have long been accepted as relatively low, 3–5%, as shown in table 1. Recently, based on 330 AVM patients treated by Gamma Knife radiosurgery (GKRS), Liscak et al. [20] reported a complication rate of 7.3%. However, we recently documented that complication rates, particularly during the longer-term follow-up period after SRS, are not as low as previously thought [21]. In this report, our experiences with 181 consecutive patients who underwent GKRS for AVMs during an approximately quarter century period from 1978 to 2002 will be summarized along with much of what we have learned from a wealth of already published data. In particular, the authors address complications occurring many years after SRS as well as their pathogeneses.

### Histopathological Changes after Stereotactic Radiosurgery and Pathogenesis of Complications

Although SRS-induced histopathological changes resulting in AVM obliteration with a 2- to 3-year latency period are detailed in the next report, we will briefly summarize them here to facilitate understanding of the pathogenesis of post-SRS complications.

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**Table 1. Incidences and latency periods of complications after irradiation**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients n</th>
<th>Patients with complications n</th>
<th>Latency periods months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear accelerator system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colombo et al. [6]</td>
<td>180</td>
<td>9 (5.0%)</td>
<td>2–18</td>
</tr>
<tr>
<td>Friedman et al. [8]</td>
<td>158</td>
<td>5 (3.2%)</td>
<td>11–15</td>
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<tr>
<td>Gamma Knife</td>
<td></td>
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<tr>
<td>Steiner et al. [17]</td>
<td>1,000</td>
<td>35 (3.5%)</td>
<td>4–56 (mean, 9.9)</td>
</tr>
<tr>
<td>Lunsford et al. [11]</td>
<td>227</td>
<td>10 (4.4%)</td>
<td>4–18</td>
</tr>
<tr>
<td>Yamamoto et al. [18]</td>
<td>121</td>
<td>6 (5.0%)</td>
<td>less than 601</td>
</tr>
<tr>
<td>Yamamoto et al. [19]</td>
<td>885</td>
<td>24 (2.7%)</td>
<td>4–24 (mean, 12.2)</td>
</tr>
<tr>
<td>Liscak et al. [20]</td>
<td>330</td>
<td>24 (7.3%)</td>
<td>6–57 (median, 13.5)</td>
</tr>
<tr>
<td>Present study</td>
<td>181</td>
<td>15 (13.6%)</td>
<td>9–215 (mean, 105)</td>
</tr>
</tbody>
</table>

1Although the latency period was not available, the maximum follow-up period in this series was 60 months.

2In 1 patient who experienced radiation-induced injury of the pons 19 months after radiosurgery, a second ictus occurred 81 months after Gamma Knife radiosurgery.
The SRS-induced changes within an AVM are considered to occur as follows: a beam of ionizing radiation initially injures the endothelial cells of vessels, thereby inducing, as a reparative process, a gradual thickening of connective tissue, which leads to accumulation of myofibroblasts, histiocytes, collagen and variable amounts of fibrin within the vessel wall. This process eventually obstructs the lumina of the AVM vessels [22]. Szeifert et al. [23] reported that these stromal cells demonstrated marked immunohistochemical positivity for smooth muscle actin (SMA) while being somewhat less positive for vimentin and desmin. Therefore, Szeifert et al. concluded, based in part on electron-microscopic observations, that the contractile activity of myofibroblasts could be relevant to the process of shrinkage and eventual occlusion of AVMs after radiosurgery. However, we previously found that, despite the remarkable positivity for SMA demonstrated immunohistochemically in patent vessels, completely obliterated vessels within the treated nidus showed no SMA staining whatsoever [24, 25]. The role of myofibroblasts, which appear to play a major part in postradiosurgical nidus obliteration, was therefore considered to be limited to the early stage of the nidus obliteration process.

Schneider et al. [26] categorized obliteration processes in radiosurgically treated AVMs into three stages: ‘endothelial or subendothelial damage’, ‘proliferation of intimal smooth muscle cells’ and ‘cellular degeneration and increased matrix’. The first stage was evidenced by a denuded endothelium or by disruption and separation of the endothelial lining from the underlying vessel walls. In the second stage, proliferation of smooth muscle cells around most or the entire wall circumference produced concentric or eccentric narrowing of the vessel lumina. The proliferative zone was immunohistochemically positive for SMA and collagen type IV (basement membrane type) while being negative for collagen types I and III (fibrillary structure types). In the third stage, cellular degeneration was evidenced by nuclear pyknosis and decreased cell number, most vessels had undergone obliteration of the entire vascular structure, with more or less uniformly dense hyalinization, and these changes were accompanied by loss of SMA and collagen type IV immunoreactivities. Our observations support their results; similar findings were obtained, particularly in the second and third stages [24, 25].

As described above, angiographically confirmed AVM obliteration does not mean total elimination of the nidus in the irradiated area; rather, it is SRS-induced tissue degeneration, consisting mostly of collagen fibers, which remains [24]. Such tissues are considered to gradually undergo liquefaction necrosis, resulting in vacuolation or collapse in most SRS-treated AVMs. However, although the underlying mechanism has not yet been fully clarified, this collagen tissue lesion persists and can even grow for many years after SRS in some cases. Usually, such a lesion is detected as a long-existing enhanced area on magnetic resonance images. Also, these lesions exude serous fluid into the surrounding normal brain tissue, thereby producing perilesional edema and/or cyst formation. Furthermore, this type of lesion undergoes neovascularization characterized by fragile vessel walls and repeated hemorrhage. This is considered to be the pathogenesis of chronic encapsulated hematoma or symptomatic hemorrhage occurring after complete nidus obliteration has been confirmed [27].