REVIEW ARTICLE
J Korean Neurosurg Soc 39 : 1-10, 2006

Gamma Knife Radiosurgery for Arteriovenous Malformations : Past Hope and Present Reality

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Introduction

Three treatment modalities, microsurgery, embolization and radiosurgery, are now available for patients with cerebral arteriovenous malformations(AVMs). With recent advances in both pre-operative and intra-operative neuro-imaging, as well as microsurgical instruments and techniques, neurosurgeons can resect many AVMs completely with an acceptably low morbidity rate. This is unquestionably ideal. Nevertheless, some AVMs cannot be resected safely even by the most experienced neurosurgeon because of their location in or near a critical brain structure or because the patient has contraindications for general anesthesia. The role of embolization is considered to be relatively small in the management of AVM patients because only 10~20% of AVMs are completely curable using this technique[27,47]. However, the role of embolization as a pre-radiosurgical procedure has been controversial. Recently, Andrade-Souza et al[2] reported that embolization prior to radiosurgery significantly reduced the obliteration rate for AVMs. In contrast, radiosurgery is widely accepted as an alternative to microsurgery in the treatment of AVMs, particularly in deep brain locations (i.e., brain stem, basal ganglia or thalamus) or critical lobar areas (i.e., sensorimotor, speech or visual cortex)[3,53]. It is clear that angiographic nidus obliteration, which has been considered to eliminate the risk of hemorrhage as effectively as surgical resection, can be achieved in 80~90% of cases with a two-three year latency period for small AVMs (< 2cc) treated with an optimal irradiation dose (> 20Gy) at the nidus margin. In such cases, the risk of irradiation-related complications is acceptably low (< 3.0%).

The availability of three different treatment modalities leads to complexity in deciding whether a single procedure, and if so which one, or a combination of two or even all three procedures should be used[16]. Whichever modality is chosen, microsurgery, radiosurgery or embolization, we should always keep in mind that palliative treatment cannot prevent bleeding and may even worsen the post-treatment course as compared with the natural history of an AVM, as recently reported by Miyamoto et al[30].

Though a comprehensive review is beyond the scope of the present article, the authors' personal experiences with 103 consecutive patients who underwent GK radiosurgery for AVMs during the more than two decade period from 1978 through 2000, will be summarized along with much of what we have learned from a wealth of already published data. In particular, the authors address the following four major questions about AVM GK radiosurgery; 1) are reported obliteration rates of 3% true? 2) are reported (re-)bleeding rates, before confirmed nidus obliteration, of 3~5% true? 3) are reported complication rates of 3% true? and 4) does angiographically confirmed nidus obliteration completely eliminate the risk of hemorrhage? The authors believe, based on very long-term follow-up results disclosed quite recently, that we have learned the radiosurgical reality on AVMs far better than those of other intracranial pathologies.

History of AVM Radiosurgery

The GK was initially used primarily for functional neurosurgical cases by the late Professor Lars Leksell. Cerebral AVMs have, however, become the most common indication for this treatment over the three decades since the early 1970s[43]. Most notably, after a redesigned second GK gained routine clinical acceptance at the Karolinska Hospital, Stockholm, in 1975, Steiner and his colleagues, particularly Lindquist and Karlsson, greatly expanded the role of GK radiosurgery in the treatment of AVMs and they had treated more than 1600 AVM patients as of June 1992. Nevertheless, there is no question

• Received : November 6, 2005 • Accepted : December 5, 2005
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that the first North American GK installed at the University of Pittsburgh in 1987, opened a great epoch in GK radiosurgery. Lunsford and his co-workers, particularly Kondziolka and Pollock, again expanded GK radiosurgery, which was a relatively new treatment procedure then, to not only the neurosurgical community in the USA but also the rest of the world. There has been an explosive increase in the number of GK sites worldwide since the early 1990s after a two decade incubation period, undoubtedly attributable primarily to the long-term efforts of the Karolinska group. However, this remarkable expansion of GK radiosurgery could not have been realized without the decade-long contributions of the Pittsburgh group.

Success in radiosurgery using a GK has prompted many investigators to modify existing linear accelerator systems to deliver higher doses of radiation to small target volumes in a single session. Colombo, Friedman and their colleagues were truly innovative pioneers in linear accelerator-based stereotactic radiosurgery for AVMs[5,6,11,12]. These two groups proved, based on their relatively large series of patients and sufficiently long follow-up results, that their systems had essentially the same effectiveness in AVM radiosurgery as the GK. This form of radiosurgery has recently developed into quite a novel frameless system using robotic techniques, the "Cyber knife[1]." The present authors, however, consider it crucial to delay final evaluation of this system until sufficiently long-term follow-up results have been accumulated.

Recent Advances in GK Technology

As the GK has undergone little modification since the mid-1970s, models A, B (U; used only in the USA) and C, there have been no major changes in either the machine itself or the stereotactic coordinate frame. The reader is thus referred to Steiner's publication for a full description[46]. The only significant development in the last ten years has been in the dose planning computer system, the GammaPlan (Leksell GammaPlan manufactured by Elekta Instruments AB, Stockholm, Sweden). Particularly in AVM GK radiosurgery, due to the remarkable development of a distortion correction technique, digital subtraction angiography(DSA) is now available for dose planning. With the new system, dose planning is always performed based on DSA as well as three-dimensional CT and/or MR images; these images are transferred very quickly to the workstation through an on-line network system. Both hardware and software for the GammaPlan are still advancing remarkably, ver. 5.20 is presently available. Furthermore, multiple isocenter treatments allow better conformity between the size and shape of the lesion and the dose distribution. Thus, we can anticipate more precise and safer treatment using these techniques, thereby lowering morbidity and possibly improving results.

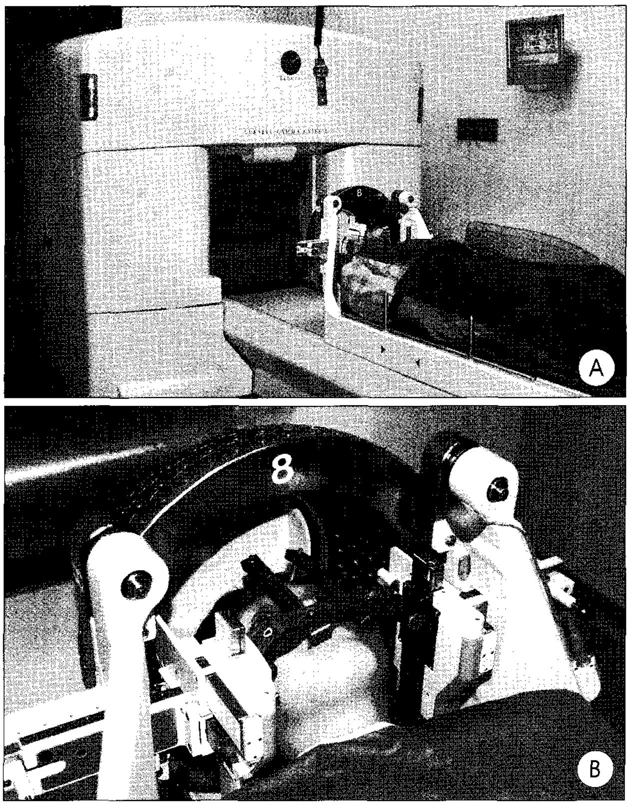

Fig. 1. Leksell gamma knife model C at the Katsuta Hospital Mito GammaHouse since July 1, 2003 (Elekta Instruments AB, Stockholm, Sweden).

Although this modification is not particularly revolutionary, the Leksell GK model C became available a few years ago. There are no significant differences in the basic structures of models B and C. With model C, once a patient's head is fixed at the first target point, subsequent target points are fixed by means of an automatic positioning system (Fig. 1). Therefore, model C remarkably reduces the lower probability of human error, increases comfort for both the patient and medical staff, and reduces treatment time. However, there is a slight chance that such a mechanical treatment procedure would depersonalize the relationship between patient and doctor, as conversing with patients and observing their conditions during each position change can be important.

Histopathology of AVMs after Radiosurgery

Radiosurgical treatment can result in AVM obliteration, after a two to three year latency period in most cases[3,5-8,11,12,21,22,26,28,34,35,38,40-42,45,53]. This radiosurgically induced change within an AVM is considered to occur as follows : a beam of ionizing radiation initially injures the endothelial cells of vessels, which induces, as a reparative process, a gradual thickening of connective tissue, which includes myofibroblasts, histiocytes, collagen and variable amounts of fibrin, within the vessel wall. This process eventually obstructs the lumina of the AVM vessels[4]. However, little information is available on the connective tissue stroma that may play an important role in the obliterative process occurring within irradiated AVMs. Szeifert et al[46] reported that the immunohistochemical reactions of these stromal cells demonstrated marked 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, the authors 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[48,51]. The role of myofibroblasts, which appear to play a major part in postradiosurgical nidus obliteration, were therefore considered to be limited to the early stage of the nidus obliteration process.

Recently, Schneider et al[39] 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 all of the 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 type). 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. The authors' observations support their results; similar findings were obtained, in particular, in the second and third stages. Furthermore, although the pathological significance is uncertain, the above-mentioned investigations revealed SMA and collagen type IV immunoreactivities to be replaced with collagen types I and III immunoreactivities in relation to the progression of obliteration[48,51].

Treatment Results

Rates of angiographically confirmed obliteration

In the historical reports from the Karolinska group[46], nearly 90% angiographically confirmed nidus obliteration rates were achieved 2-3 years after GK radiosurgery. These relatively high obliteration rates became increasingly generalized in the neurosurgical field until the mid-1990s. However, as professor Steiner always noted in his lectures, the obliteration rate of 90% was achieved only in patients whose nidi were sufficiently small. In contrast, relatively large AVMs are treated with a GK in actual neurosurgical practice, and, therefore, the obliteration rate inevitably decreases.

Angiographically confirmed nidus obliteration is reportedly achieved in 70~80% of AVM patients undergoing radiosurgery using a GK, a linear accelerator based system or a particle beam system. However, as Friedman et al[12] pointed out, the reported percentages of angiograms showing complete thrombosis do not give a complete picture of outcomes for radiosurgically treated AVM patients. Almost all published obliteration rates were based on the special group of patients who underwent follow-up angiography. In fact, the lack of data on the entire GK-treated AVM population is a major criticism of GK radiosurgery for AVMs. Now that MR imaging has become widespread and has advanced remarkably during the past 15 years, most AVM patients have been checked after GK radiosurgery with an interval of 6 or 12 months. DSA is usually performed only for patients whose AVMs were suggested to be obliterated on follow-up MR images. The authors consider it absolutely crucial to know what happened in the remaining patients.

Therefore, the authors have described all obliteration rates based on the entire group of treated patients. One of the authors reported the overall obliteration rate to be approximately 65% for the entire group (of 40 patients) in whom meticulous follow-up was possible[50]. In another publication, based on a total of 885AVM patients treated at the 11GK facilities in Japan, the overall obliteration rate, 50%, after a single course of irradiation seems low[52]. This is due to the rate being based on the entire group of patients; this obliteration rate corresponds to 65% of the 681 patients who underwent angiography. Also, the authors recently analyzed 103 patients, as described earlier. Complete obliteration was achieved in 55 (53%) of the 103; 55 (64%) of 86 who underwent DSA.

Whether obliteration of a radiosurgically treated AVM is permanent has long been a central question. According to Lindqvist et al's recent report[25], among 48 patients who underwent angiography 5 to 24 years after GK radiosurgery and 4 to 17 years after the AVMs had been proven to be occluded, recanalization was demonstrated in four; there was evidence of AVM nidi at the sites of previously occluded AVMs in two, while two others had nidi adjacent to such sites. The recurrent AVMs manifested with hemorrhage in three of the four patients; these three patients were 14 years of age or younger at the time of GK radiosurgery. These results show that there is a slight possibility of AVMs reappearing after having shown complete occlusion following radiosurgery, especially in pediatric patients. Interestingly, a similar condition, AVM recurrence, has been reported in pediatric patients in whom microsurgical resection of AVMs had been successful[17].

Treatment failure and re-treatment

Pollock et al reported four factors associated with successful AVM radiosurgery; smaller AVM volume, fewer draining veins, younger patient age and hemispheric AVM location. Conversely, in patients with AVMs showing the opposite features, an insignificantly low incidence of treatment failure may be expected. As Pollock et al[32,33] and Gallina et al[13] reported, there are five primary causes of treatment failure 1. Inadequate nidus visualization at the time of radiosurgery, 2. Recanalization of a previously embolized AVM, 3. Improper assessment of the three-dimensional AVM shape, 4. Delivery of an insufficient radiation dose, and 5. Radiobiological resistance of the AVM, which is only speculative.

A second course of radiosurgery is required for patients in whom complete nidus obliteration is not attained after the initial treatment because even a very small residual nidus has the potential to bleed. A second radiosurgery is usually performed more than three years after the first procedure. Karlsson et al[18] reported that the obliteration rate after the second course of radiosurgery was similar to that after primary treatment, but that there was a significantly higher risk for complications; 14 radiation-induced complications occurred while the expected number of complications, calculated using a risk estimation model after single treatment, was five. In fact, the authors experienced two patients with severe complications after two courses of GK radiosurgery, as shown in Fig. 2, 3.

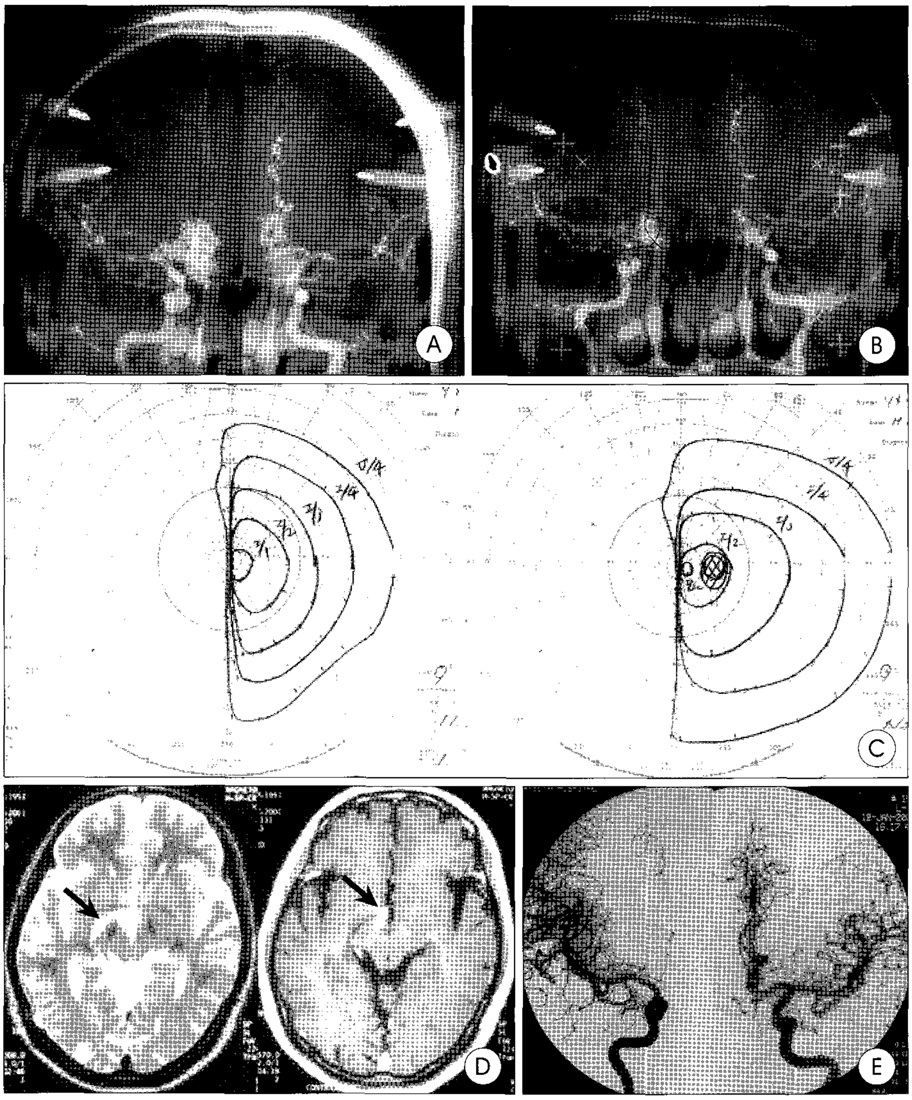

Fig. 2. Sequential right and left carotid angiograms obtained in an AVM patient at the time of the first radiosurgery (A) and at the time of the second radiosurgery (B); the interval between the two procedures was 43 months. The nidus was irradiated with a dose of 16.67Gy at the periphery at the time of the first treatment and the residual AVM was re-irradiated with a dose of 14.00Gy at the periphery. This patient experienced left homonymous hemianopsia 12 months after re-irradiation (C) and a magnetic resonance image demonstrated abnormal enhancement of the right optic tract (D, arrows). Complete nidus obliteration was angiographically confirmed 76 months after the first GK (E).

Seizure and headache control

Although the most common manifestation of cerebral AVMs is intracerebral hemorrhage, the second most common presentation is epileptic seizure. Steiner et al[44] reported that 41 (69.4%) of 59 AVM patients with seizures became seizure-free or experienced significant improvement after GK radiosurgery. Recently, Kurita et al[23] reported similar results; 28 of 35 patients with unruptured epileptogenic AVMs remained seizure free at the time of final follow-up, the mean of which was 43 months after GK radiosurgery. They also described the frequency of seizures as beginning to decrease several months before neuroimaging examinations demonstrated changes in the nidus.

Headache is the third most common symptom of cerebral AVMs. Steiner et al[44] reported that, among

98 AVM patients with chronic headache, this symptom disappeared entirely or improved significantly in 74 (75.5%) after GK radiosurgery. Recently, Kurita et al[24] analyzed 37 patients with migraine-like headache, who underwent GK radiosurgery for occipital AVMs. According to their results, headache resolved in 70.6% of patients and amelioration correlated closely with nidus obliteration.

Riva et al recently reported that radiosurgical treatment for AVMs did not influence postradiosurgical neurobehavioral outcomes in pediatric patients. Rather, the less invasive nature of this treatment appeared to have contributed to the patients' good physical, mental and emotional outcomes.

(Re-)Bleeding

As shown in Table 1, (re-)bleeding during the latency period, the incidence of which varied from 2.7% to 11.6%, has been recognized in major reported series on radiosurgery using a GK[21,28,34,35,38,45,46,52,53], a linear accelerator system[3,5,6,11,12,26,40] or a particle beam system[7,8,22,41]. Steiner et al.[46] reported the overall risk of this complication to be 3.4% at 36 postradiosurgical months. Karlsson et al.[20] reported that, in 49 of their 1604 AVM patients treated with GK radiosurgery, hemorrhage occurred during the first two postradiosurgical years and that an additional 41 patients experienced hemorrhage more than two years after treatment. Following (re-)bleeding during the latency period, mortality rates of approximately 30% were reported in relatively large patient series. In the authors' experience as well, (re-)bleeding during the latency period occurred in nine (8.7%) of 103 patients, resulting in death in five, severe disability in two, and moderate disability and no additional deficits in one each.

Pollock et al.[31] reported that radiosurgery conferred no protective benefit for patients in whom nidus obliteration was incomplete. However, Karlsson et al.[20] reported that the calculated incidence of this complication was roughly double that observed in untreated AVM patients. Very recently, Maruyama et al[29] reported that the pre-obliteration bleeding rate was significantly lower than that associated with the natural course. This issue, i.e. whether radiosurgical treatment can prevent AVM rupture even if the treated nidus is not completely obliterated, remains controversial. Based on the current evidence, however, the authors are confident that stereotactic radiosurgery does not increase the risk of AVM hemorrhage during the latency period preceding obliteration. The observation that, fortunately, the incidence of this complication after GK radiosurgery is low makes it difficult to assess quantitatively the influence of various factors on the risk

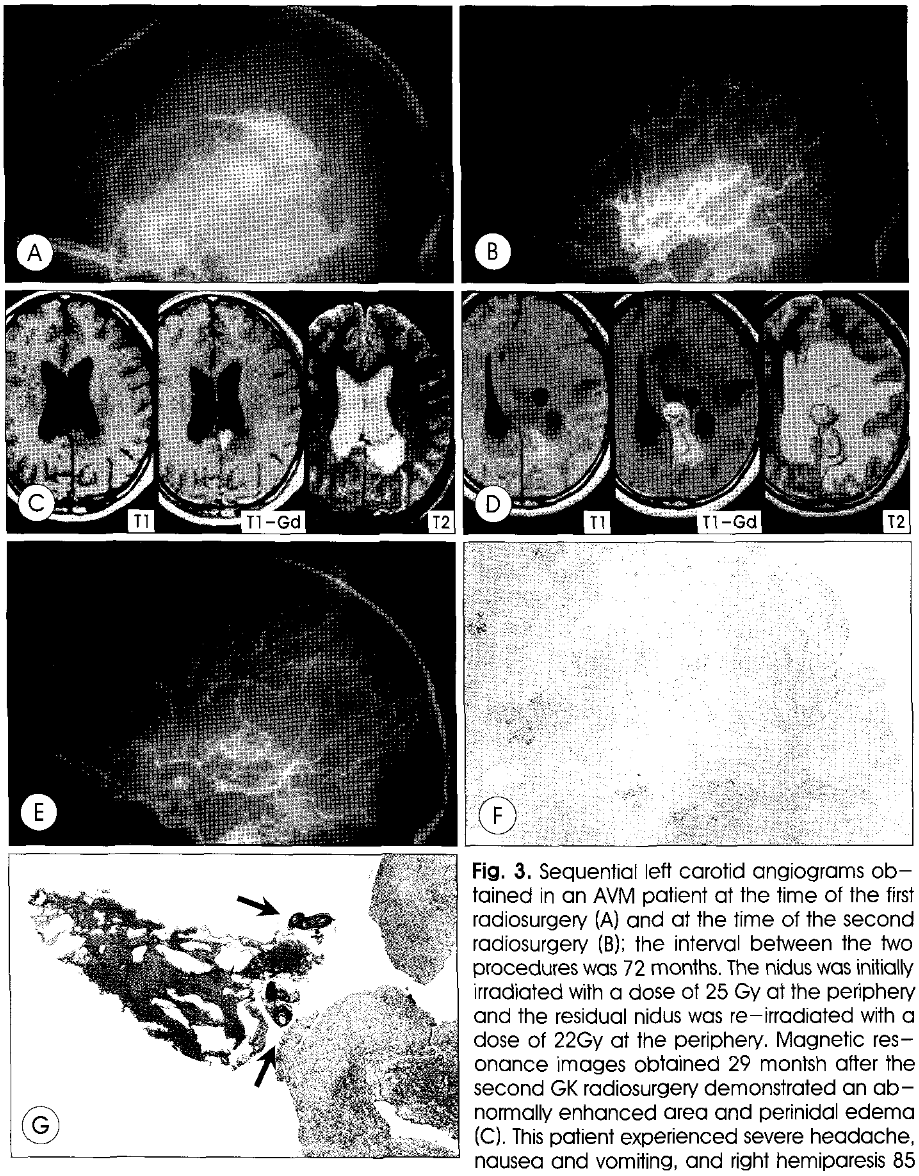

Fig. 3. Sequential left carotid angiograms obtained in an AVM patient at the time of the first radiosurgery (A) and at the time of the second radiosurgery (B); the interval between the two procedures was 72 months. The nidus was initially irradiated with a dose of 25 Gy at the periphery and the residual nidus was re-irradiated with a dose of 22Gy at the periphery. Magnetic resonance images obtained 29 montsh after the second GK radiosurgery demonstrated an abnormally enhanced area and perinidal edema (C). This patient experienced severe headache, nausea and vomiting, and right hemiparesis 85 months after re-irradiation. Magnetic resonance images demonstrated an abnormally enhanced area, cyst formation and diffuse white matter edema (D). Angiograms demonstrated no vascular abnormalities (E). Cyst evacuation and partial removal of the enhanced mass were carried out. Pathology showed that the mass consisted of a matured collagen tissue and that there were a few degenerative vessels (F; HE and G; EvG, arrows).

Table 1. *Incidences and latency periods of (Re-)bleeding after irradiation*

Authors	No. of patients	No. of patients with bleeding	No. of patients with fatal bleeding	Latency periods (months)
Linear accelerator system				
Colombo et al[16]	180	15(5.0%)	5	6~24
Friedman et al[10]	158	6(3.8%)	1	2~11
Particle beam system				
Kjellberg et al[12]	75	2(2.7%)	2	less than 12
Steinberg et al[19]	86	10(11.6%)	2	4~34 (mean; 12.8)
Gamma knife				
Karlsson et al[46]	1604	90(5.6%)	14/49	24 or less; 49 patients more than 24; 41 patients
Lunsford et al[14]	227	10(4.4%)	2	maximum 23?
Yamamoto(Y) et al[22]	121	7(5.8%)	3	3~30
Yamamoto(Y) et al[34]	858	41(4.6%)	13	1~48(mean;16.3)
Present study	170	11(6.5%)	4	2~66(mean;18.3)

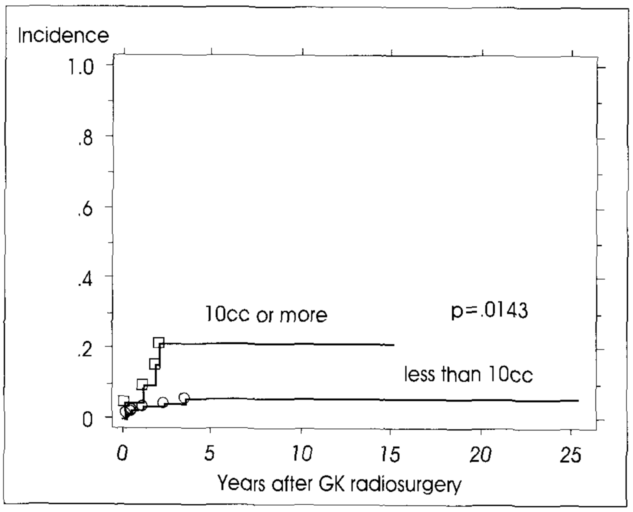

Fig. 4. Cumulative Incidences of Bleeding During Latency Period : Nidus Volume.

of hemorrhage[10,31]. Johkura et al[15]. recently reported that the only factor allowing prediction of a higher risk of bleeding was larger AVMs. The authors also experienced, based on 170 AVM patients who had been followed more than three years after GK radiosurgery, nidus volumes of 10cc or more to be associated with a significantly higher incidence of bleeding than those smaller than 10cc (p=.0143), as shown in Fig. 4.

It is clear that angiographically demonstrated nidus obliteration eliminates the risk of hemorrhage in the vast majority of patients. However, as reported previously, the authors experienced one patient who likely suffered a symptomatic hemorrhagic stroke 5 years after 2-year postradiosurgical angiography had demonstrated complete obliteration[50]. Furthermore, as shown in Fig. 3, 5, the authors recently experienced two additional patients with intracerebral hemorrhages which developed, respectively, 12 and 15 years after GK radiosurgery despite post-GK angiography having shown complete nidus obliteration. The recently published data of Maruyama et al support the authors' results[29].

Delayed Radiation-induced Complications

Delayed radiation-induced complications reportedly occur in 3.2~12.5% of patients with radiosurgically treated AVMs[3,5-8,11,12,21,22,26,28,34,35,38,45,46,52,53] (Table 2). It is widely accepted that the dose-volume relation is the most important factor influencing the risk for delayed complications after radiosurgery; the larger the nidus volume is or the higher the doses used, the greater the increases in complication risks. Flickinger et al[9] reported that, among 30 patients who sustained postradiosurgical complications, symptoms resolved in 58% within 27 months with a significantly greater proportion resolving in those receiving less than 20Gy at the nidus periphery as compared with those receiving more than 20Gy (89% vs 36%, p=0.006). The second important factor is how much normal brain volume is included within the target volume. As described above, however, the most recent dose planning techniques allow us to avoid excess irradiation to the normal brain, which can be expected to significantly reduce the risks for delayed complications. Likewise, as with the postradiosurgical hemorrhage mentioned above, the fact that the incidence of this complication after GK radiosurgery is fortunately low makes it difficult to assess quantitatively the influences of various factors. Karlsson et al[19], using their own risk estimation model, found that centrally located AVMs had a higher, and peripheral a lower incidence of complications, and that a previous hemorrhage reduced the risk, as compared with estimates made with their model. According to a multi-institutional analysis of complication outcomes reported by Flickinger et al[9], significantly greater symptom resolution was observed in patients with no prior history of hemorrhage and in those with symptoms of minimal severity.

The majority of radiation-induced complications occur by the third postradiosurgical year. However, the authors and colleagues previously reported[50] two patients (5.3%) who experienced symptomatic complications which developed more than five years after irradiation. Recent analysis of our personal series of 103 AVM patients who have been followed for at least five years (5.0~26.5 years, mean; 10.3 years) since GK radiosurgery disclosed 14 radiation-related morbidities (13.6%), eight of which manifested five years or more after radiosurgery and four 10 or more years later. In the authors' series, the

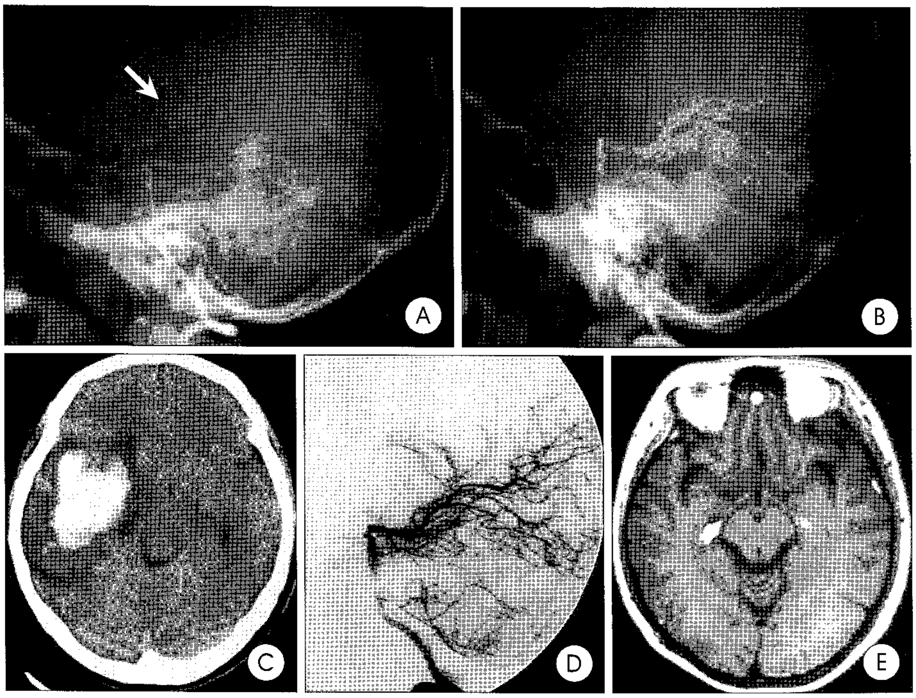

Fig. 5. Sequential vertebral angiograms obtained in an AVM patient at the time of (A) and 12 months after (B) radiosurgery. Although the treated nidus (arrow) had been invisible on an angiogram obtained 12 months after irradiation, this patient sustained an intracerebral hematoma which developed 191 months after radiosurgery, as shown on computed tomographic scan (C). Angiography demonstrated no vascular abnormalities (D). Surgical removal of the hematoma was required. Retrospectively, a magnetic image obtained 84 months after GK radiosurgery showed that nidus enhancement persisted (E).

cumulative complication rates computed using the Kaplan-Meier method were 6.2% at the 5th, 13.7% at the 10th, 22.8% at the 15th and 27.0% at the 20th post-GK year (Fig. 6). In one of the seven patients, who experienced radiation-induced injury of the pons 19 months after radiosurgery, a second ictus occurred at 81 post-GK months. The authors also experienced five patients in whom, despite remaining asymptomatic to date, radiation-related adverse effects were seen on neuro-imaging between 5 and 10 post-GK years; cyst formation in three and stenosis of a major artery and appearance of dural arteriovenous fistula in one each[49]. Furthermore, Sakaki et al[37] recently presented an AVM patient, with a very disturbing outcome; the patient underwent GK radiosurgery and ultimately died due to glioblastoma multiforme that initially appeared at the target area several years after irradiation.

How to Treat a Relatively Large AVM with Radiosurgery

Although optimal doses for nidus obliteration are widely considered to be between 18 and 25 Gy at the nidus periphery, the treatment dose for each patient is decided considering the nidus volume and neighboring brain structures; if, despite the absolute volume being small, the nidus is located in, or close to, critical brain structures, such as the cranial nerves, the brain stem, and so on, a decrease in the dose is required considering the upper dose limit for risks of complications involving each structure. In such cases, staged

Table 2. Incidences and latency periods of complications after irradiation

Authors	No. of patients	No. of patients with complications	Latency periods (months)
Linear accelerator system			
Colombo et al[6]	180	9(5.0%)	2~18
Friedman et al[10]	158	5(3.2%)	11~15
Souhami et al[18]	33	3(10.0%)	6,7and9
Particle beam system			
Kjellberg et al[12]	75	8(10.7%)	not available
Steinberg et al[19]	86	17(19.8%)	3~33(mean;13.4)
Gamma knife			
Steiner et al[26]	1000	35(3.5%)	4~56(mean;9.9)
Lunsford et al[14]	227	10(4.4%)	4~18
Yamamoto(Y) et al[22]	121	6(5.0%)	less than 60*
Yamamoto(Y) et al[34]	885	24(2.7%)	4~24(mean;12.2)
Present study	103	14(13.6%)	9~188(mean;78)**

*Although the latency period was not available, the maximum follow-up period in this series was 60 months. **In one patient who experienced radiation-induced injury of the pons 19 months after radiosurgery, a second ictus occurred at 81 post-GK months

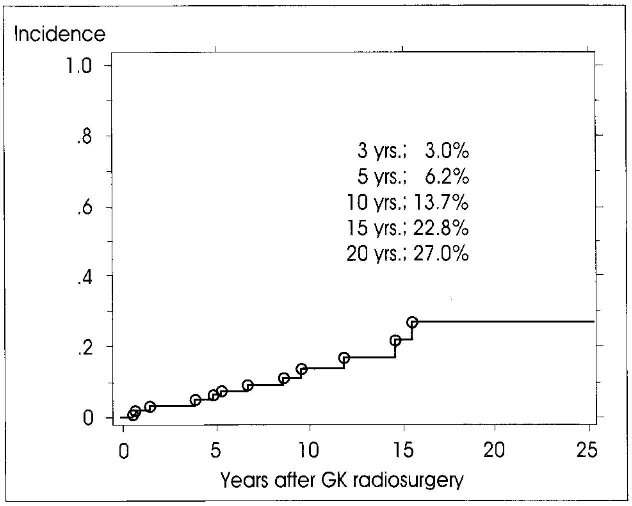

Fig. 6. Cumulative Incidences of Radiation-Induced Complications after GK Radiosurgery.

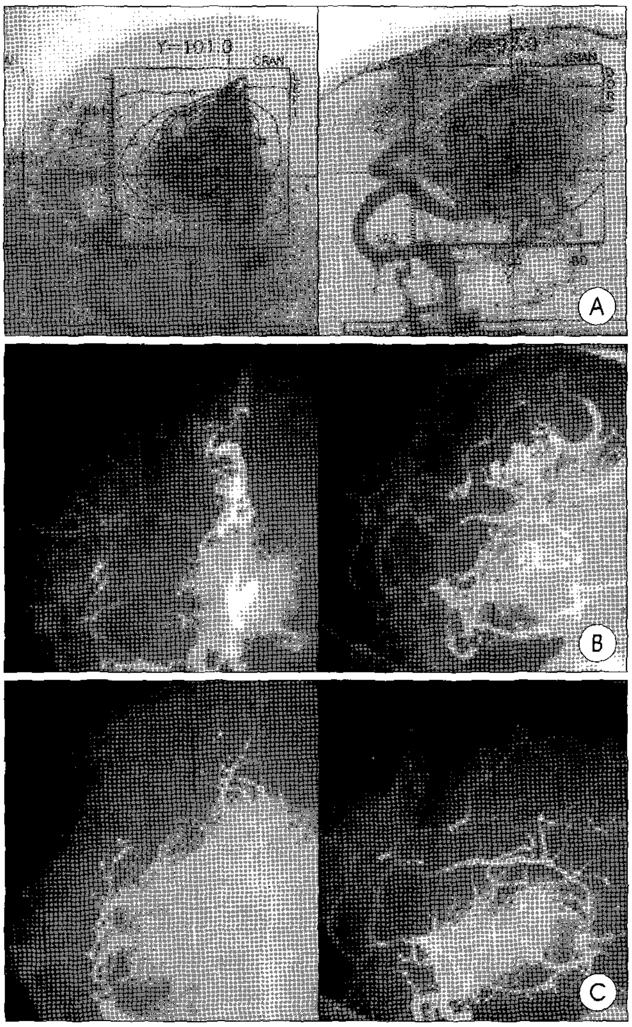

Fig. 7. Sequential right carotid angiograms obtained in an AVM patient at the time of (A : isodose gradient superimposed, left; anterior-posterior view and right; lateral view), 36 months after (B : before the second treatment, left; anterior-posterior view and right; lateral view), and 73 months after (C : 36 months after the second radiosurgery, left; anterior-posterior view and right; lateral view) the first radiosurgery. The nidus with a volume of 17.8cc was intentionally irradiated with a low dose (14Gy at the periphery) at the time of the first treatment. Three-year postradiosurgical angiography demonstrated remarkable nidus shrinkage but there was a small residual nidus. This residual AVM was re-irradiated with a dose of 20Gy at the periphery using a gamma knife and further follow-up angiography demonstrated complete nidus obliteration three years after the second radiosurgery (six years after the first treatment).

radiosurgery, a volume fraction or a dose fraction, has been applied. The authors have abandoned volume-fractionated radiosurgery for relatively large AVMs, in which the nidus is divided into two or three compartments using selective angiography, and one compartment is irradiated first and then the remaining part with an appropriate interval. This was done because, in the authors' early experiences with three patients using this technique, the treatment results were quite unfavorable. Massive hemorrhage occurred in one patient who eventually died, while complete obliteration was achieved but severe symptomatic complications occurred in another who eventually committed suicide. A good outcome (complete nidus obliteration without adverse effects) was achieved in the sole remaining patient. Therefore, although a final conclusion is several years down the road, instead of a volume-fractionated technique, dose-fractionated radiosurgery may be recommended for patients with relatively large AVMs. With this technique, as shown in Fig. 7, the entire nidus is treated with a relatively low dose (12~16Gy at the nidus periphery) during the first procedure, followed by a second procedure for the residual nidus 3 years later. The authors applied this technique in 24 patients during a 15 year period (1988~2003) and recently analyzed interim results. Fourteen of the 24 patients underwent a second procedure. Six of the 14 underwent DSA 3 years or more after the second GK treatment. Complete nidus obliteration was confirmed in five and nearly complete obliteration in one. The crucial points of this technique are higher rebleeding rates and a possibly higher risk of complications. Six patients (25%) experienced bleeding after the first GK treatment; thee mortalities, two morbidities. In fact, only one patient (4.2% of the 24) experienced a treatment-related complication (complete hemianopsia), 24 months after the second GK procedure (Fig. 2). However, the complication rates were 7.1% and 16.7%, respectively, based on 14 receiving a second treatment and 6 ultimately examined using DSA. In one of the latter patients, the nidus was angiographically confirmed to show complete obliteration and no hemorrhage has occurred in the 6.5 years to date since the second treatment. However, this patient experienced CT-demonstrated (non-symptomatic) hemorrhage three times before the first GK radiosurgery and then three more times between the first and the second GK treatments. Considering that the nidus location (involving the optic chiasma and the hypothalamus) made it inaccessible to either surgery or other interventional approaches, total management was not thought to have resulted in a poor outcome in this case, despite the tragic occurrence of the aforementioned complication and the treatment strategy not having been completely successful.

Conclusions Based on Personal Experiences

Although GK radiosurgery is undoubtedly an alternative to microsurgical resection for appropriately selected AVMs, we should weigh treatment results against cumulative management risks which are not negligibly low. Long-term follow-up data (mean; 10.3 years, range; 5.0 to 26.5) from our consecutive series of 103 patients with AVMs who underwent GK radiosurgery during the period from 1978 through 1999 were reviewed. Using the Kaplan and Meier method, actual rates for

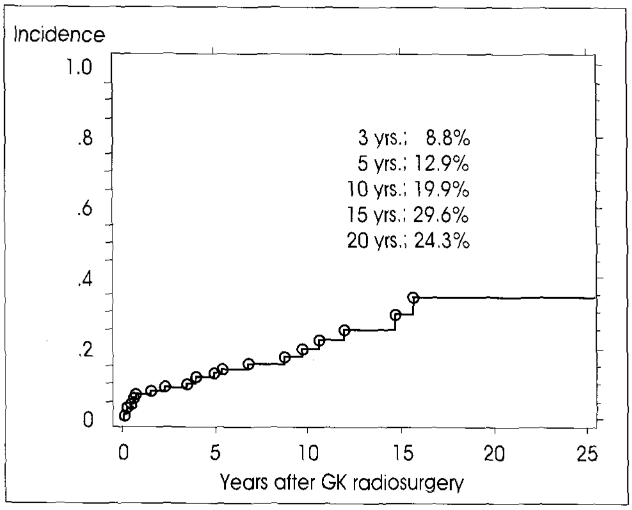

Fig. 8. Cumulative Incidences of Management Complications (Bleeding and Radiation-Induced Complications) after GK Radiosurgery.

total management complications, including bleeding during the latency period and radiation- and/or treated-AVM-related adverse effects, were 13.9%, 20.8% and 30.5% at the 5th, 10th and 15th post-GK years, respectively (Fig. 8). However, the incidences at more than ten years after GK radiosurgery are obviously overestimated because of the small sample size for this period. Nevertheless, the next question is whether GK radiosurgery, despite the procedures undoubtedly being less invasive, constitutes a dangerous treatment for patients with AVMs. The reader should keep in mind that approximately one-third of the patients described herein had radiosurgery early in the "learning curve." Unfortunately, there are no published data for sufficiently long-term post-surgical follow-up. Hartmann et al[14] reported their surgical results based on 124 AVM patients who were followed relatively long-term, the mean and the maximum follow-up intervals being 1 and 9 years (still early in the radiosurgical field). They experienced six surgical mortalities (5%) and 19 patients (15%) had surgery-related neurological deficits. If these results are compared with ours, keeping in mind that most of the authors' patients did not have indications for surgery, GK radiosurgery is apparently not a dangerous procedure for AVM patients.

Nevertheless, some anxiety persists regarding the use of irradiation in young patients with benign lesions such as AVMs. It is essential for radiosurgeons to determine, based on very large patient series with 10~20 year follow-up, the actual incidences of very rare post-radiosurgical complications such as tumor neogenesis, cyst formation, major vessel obliteration, radionecrosis, and so on.

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