


Gamma Knife Radiosurgery For Brain Vascular Malformations: Current Evidence And Future Tasks

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Abstract: Gamma Knife radiosurgery (GKRS) has long been used for treating brain vascular malformations, including arteriovenous malformations (AVMs), dural arteriovenous fistulas (DAVFs), and cavernous malformations (CMs). Herein, current evidence and controversies regarding the role of stereotactic radiosurgery for vascular malformations are described. 1) It has already been established that GKRS achieves 70–85% obliteration rates after a 3–5-year latency period for small to medium-sized AVMs. However, late radiation-induced adverse events (RAEs) including cyst formation, encapsulated hematoma, and tumorigenesis have recently been recognized, and the associated risks, clinical courses, and outcomes are under investigation. SRS-based therapeutic strategies for relatively large AVMs, including staged GKRS and a combination of GKRS and embolization, continue to be developed, though their advantages and disadvantages warrant further investigation. The role of GKRS in managing unruptured AVMs remains controversial since a prospective trial showed no benefit of treatment, necessitating further consideration of this issue. 2) Regarding DAVFs, GKRS achieves 41–90% obliteration rates at the second post-GKRS year with a hemorrhage rate below 5%. Debate continues as to whether GKRS might serve as a first-line solo therapeutic modality given its latency period. Although the post-GKRS outcomes are thought to differ among lesion locations, further outcome analyses regarding DAVF locations are required. 3) GKRS is generally accepted as an alternative for small or medium-sized CMs in which surgery is considered to be too risky. The reported hemorrhage rates ranged from 0.5–5% after GKRS. Higher dose treatments (>15 Gy) were performed during the learning curve, while, with the current standard treatment, a dose range of 12–15 Gy is generally selected, and has resulted in acceptable complication rates (< 5%). Nevertheless, further elucidation of long-term outcomes is essential.

Keywords: arteriovenous malformation, cavernous malformation, dural arteriovenous fistula, gamma knife radiosurgery, stereotactic radiosurgery

Introduction

Based on the concept of stereotactic radiosurgery that was first introduced in 1951, the gamma unit was designed by Lars Leksell using multiple ⁶⁰Co sources focused at a fixed center.^{1,2} Characterized by its single-session focused irradiation with high accuracy and sharp dose fall-off,^{3,4} gamma knife radiosurgery (GKRS) was first introduced clinically in 1968 and has since been used to treat more than one million patients worldwide with a variety of cerebral/cranial conditions.^{2,5–7} Arteriovenous malformation (AVM), dural arteriovenous fistula (DAVF), and cavernous malformation (CM) are the main GKRS targets; all are categorized as brain vascular malformations and are essentially caused by arteriovenous shunting, though their

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conditions and responses to GKRS are entirely different. Numerous studies, including systematic reviews and multicenter retrospective analyses, have examined radiosurgical outcomes of these disorders and the efficacy of GKRS has been well established. Nevertheless, several problems remain that must be addressed. Herein, we summarize current evidence supporting the use of GKRS for such brain vascular malformations and discuss persisting controversies.

GKRS Procedures For Vascular Malformations

Using local anesthesia with or without sedation, the patient's head is fixed in a Leksell Coordinate Frame G (Elekta AB, Stockholm, Sweden). The patient is then sent to a radiographic suite to undergo stereotactic imaging studies, including magnetic resonance imaging (MRI), computed tomography (CT), and digital subtraction angiography (DSA). These imaging studies are performed with fitting of an appropriate indicator on the frame, which imposes fiducials on images of the patient. The acquired image dataset is then sent to GammaPlan (Elekta AB), a radiosurgical planning software program. In creating the radiosurgical plan, an appropriate prescription dose is aimed at the target's margin usually using a 50–60% isodose gradient while a 70–90% isodose gradient occasionally is used in patients with a relatively small target. A margin, the setting of which is usually recommended in linac-based radiosurgery, is not required.

GKRS For Arteriovenous Malformation Current Evidence

Brain AVM is the most common brain vascular malformation with a prevalence of just under 10 per 100,000.^{8–10} The hemorrhage risk is reported to be approximately 3%/year. Once a hemorrhage occurs, the possibilities of neurologic deficits and death are < 50% and < 10%, respectively.^{8,11,12} Therefore, the treatment goal is to eliminate the risk of hemorrhage, which can be achieved by isolating the nidus from the circulation. GKRS is considered to be a main therapeutic modality and is often applied to small to medium-sized AVMs.^{8,13–15}

Generally, nidus obliteration can be achieved in 70–85% of patients after a 3–5 year latency period.^{15–22} Though DSA is still the gold standard method for confirming nidus obliteration, there is a recent tendency to avoid

DSA due to its invasiveness. MRI is generally regarded as an acceptable alternative, exhibiting 77–85% sensitivity and 89–95% specificity.^{23,24} Radiosurgical dose and AVM size are the factors most strongly influencing nidus obliteration.^{15–18,20,21,25–45} The Pittsburgh radiosurgical AVM score¹⁷ with its modification⁴¹ and the Virginia radiosurgical AVM scale²⁵ are two major scoring systems which aid neurosurgeons in predicting post-radiosurgical outcomes. As to disadvantages of GKRS, approximately 30% of patients suffer from perinidal T2-signal intensity change within 2 years after the procedure, but this becomes symptomatic in less than 10% and permanent in only 3%.^{15,46–51} Post-GKRS hemorrhage is rare,^{52–55} and the risk does not increase, remaining the same or decreasing during the latency period.⁵² Whether nidus obliteration means “complete” eradication of hemorrhage risk remains debatable.⁵⁶ Bleeding due to recanalization of a once-obliterated nidus, albeit quite rare, has been reported.^{57,58}

Late Radiation-Induced Adverse Events (RAEs)

Since the late 1990s, an increasing number of studies have described late RAEs, including cyst formation (CF), chronic encapsulated hematoma (CEH), and tumorigenesis.⁵⁹ Radiation-induced chronic inflammation appears to play an important role in the former two conditions,^{60,61} suggesting that target size is strongly associated with their occurrence.^{62–64} The other risk factors include lobar location, higher prescription dose, and history of embolization as pre-GKRS factors, the occurrence of early edema, additional irradiation, and the state of nidus obliteration as post-GKRS factors.^{63–71} CF/CEH develops approximately 6.5–11.8 years after irradiation, and the cumulative incidences are estimated to range from 2.8–7.7% at 10 years and 7.6–12.5% at 15 years.^{64–66,68} Though the optimal treatment remains a source of controversy, surgical resection is widely regarded as a standard option. However, fluid diversion, including cyst-peritoneal shunt and ommaya reservoir placement, are minimally invasive alternatives for exclusively cystic lesions.^{64–66,68} Oral corticosteroids may help reduce the associated edema and alleviate symptoms; however, the long-term effects remain unknown.^{64,68} Previous studies on CF/CEH are summarized in [Table 1](#).^{62–64,66–68,72–74}

Regarding radiation-induced tumorigenesis, the majority of such lesions are malignant glioma.^{64,75–79} Attempts have been made to calculate the radiation-induced tumorigenesis incidence, which has been roughly estimated to be

Table I Literature Review On Late RAEs (Studies With ≥ 100 patients)

Author	Year	N	Median Observation Period (y)	Definition Of Late RAEs	Incidence (Crude Or Cumulative Rate)	Risk Factors	Remarks/ Treatment Modality
T. Hasegawa ⁷²	2019	189	11.3*	CF, CEH, RIT	7.2%/15 y (cumulative)	Larger nidus volume	All pediatric patients.
H. Hasegawa ⁶⁴	2018	581	11.8*	CF, CEH	7.6%/15 y (cumulative)	Diameter > 22 mm, lobar location, (Early edema, secondary SRS) [†]	GKRS
Pomeraniec ⁶⁶	2018	1159	5.9 (w CF)/11.0 (wo CF)	CF	1.5% (crude)	Larger number of isocenters, early edema, longer follow-up	GKRS
Pollock ⁶⁸	2017	233	9.8	ND	12.5%/15 y (cumulative)	Early edema, nidus occlusion, SRS before April 1997	GKRS
Nakajima ⁷³	2016	404	4.9	CF, CEH	5.0% (crude)	No factor	GKRS
Matsuo ⁶⁷	2014	109	ND	CF	5.5% (crude)	NA	Linac-radiosurgery
Parkhutik ⁶²	2013	102	5.3	Radionecrosis	6.9% (crude)	Diameter > 3 cm, secondary SRS	GKRS
Pan ⁷⁴	2005	1203	See below [†]	CF	3.6% (crude)	Addition of embolization, early edema	GKRS
Izawa ⁶³	2005	237	6.8*	CF	3.4% (crude)	Higher central dose, larger nidus volume, nidus occlusion, lobar location	GKRS

Notes: *Mean. [†]Observation period < 5 y, 674 patients; 5–10 y, 332 patients; 11–15 y, 167 patients; 16–23 y, 30 patients.

Abbreviations: AVM, arteriovenous malformation; CF, cyst formation; CEH, chronic encapsulated hematoma; GKRS, gamma knife radiosurgery; NA, not assessed; ND, not described; RAE, radiation adverse event; RIT, radiation-induced tumor; y, year(S); w, with; wo, without.

less than 0.2%.^{64,75,76} The actual incidence, however, has yet to be determined due to the rarity of this condition.

Staged GKRS For Large AVMs

Large AVMs are challenging targets. Radiosurgical doses are generally reduced for fear of RAEs, which in turn could decrease the obliteration rate and might eventually result in a higher hemorrhage rate.⁸⁰ In short, it is important to balance the therapeutic effect and risks. Accumulated evidence tells us that stand-alone GKRS for AVMs > 10 mL is controversial and that staged GKRS is an alternative that is frequently considered.⁴⁹

There are two distinct staging methods: volume-staged GKRS (VSGKRS) and dose-staged GKRS. In VSGKRS, the entire nidus volume is divided into 2 or 3 parts, which are then irradiated independently with intervals of several months (usually 3 to 6 months).^{81–91} On the other hand, in dose-staged GKRS, the entire nidus is irradiated repeatedly with an attenuated dose until a planned cumulative dose has been fully delivered.^{91–94} Although no definitive

conclusion has yet been reached, retrospective evidence indicates the superiority of VSGKRS.^{95,96}

Previous studies on VSGKRS are summarized in Table 2.^{89,94,97,98–103} The crude obliteration rates after VSGKRS range between 33% and 72%, the exception being one study reporting 13%; this broad range may be due to marked differences in nidus volumes among studies (mean, 16.8–60 mL) and the wide variety of prescription doses administered (mean, 15.5–20.8 Gy).^{81–91,101} It seems that a dose of at least 17 Gy for each session is needed to obtain a favorable obliteration rate; if lesions are treated with ≥ 17 Gy, the obliteration rate approaches 60%.^{97,102} The other factors that potentially contribute to successful obliteration include larger than 20 Gy-volume coverage⁹⁷ and a single drainer vessel.⁸⁹ However, these results are not consistent and further research is needed. Regarding the disadvantages of VSGKRS, relatively high hemorrhage rates are the primary concern, with crude rates ranging from 4.5% up to 33%.^{81–91,101} The occurrence of RAEs would presumably be greatly affected by the dose, volume, location, and follow-up duration, and is thus

Table 2 Literature Review On Outcomes Of VSGKRS For Large AVMs (Studies With ≥ 15 patients)

Year	Author	N	Median Follow-up Period (m)	Median Age At GKRS (y)	Median Prescription Dose (Gy)	Median Nidus Volume (mL)	Cases With Prior Hemorrhage	Obliteration Rate	Post-GKRS Hemorrhage Rate	Morbidity	Mortality
2019	El-Shehaby ⁹⁸	29	43*	24*	18*	16*	58.3%	62.5% (CR)	2%/y	3.4% (CR)	0%
2018	Kano ⁹⁷	60	ND	30	16	11.6 (1st), 10.6 (2nd)	43%	44%/10 y	25.2%/10 y	7% (CR)	16.7%/10 y
2017	Pollock ¹⁰¹	34	98.4	31	16	22.2	35%	75%/7 y	4.6%/y	6% (CR)	6% (CR)
2017	Nagy ¹⁰³	44†	> 48	37	17.5	19.7	44%	61.4%/4 y	3.2%/y (wo HoH), 5.6%/y (w HoH)	6.5% (CR)	6% (CR)
2016	Hanakita ⁸⁹	18	53	33	16	38	67%	35%/5 y	3.9%/y	11% (CR)	5.5% (CR)
2016	Park ^{94***}	45	104.9*	29*	13–17	20.4*	22.2%	64.4% (CR)	11.1% (CR)	ND	3% (CR)
2016	Seymour ¹⁰²	69	57.6–103.2	34	15.5–17.0	18.9–27.3	35–39%	21–68%/5 y (including near complete obliteration)	5.6%/y	3–16% (CR)	13–21% (CR)
2016	Franzini ⁹⁹	20	45*	38	20	15.9	30%	20% (75% reduction)	10% (CR)	5% (CR)	ND
2012	Huang ¹⁰⁰	18	> 36‡	35	15	22.9	55.6%	89%/10 y	31%/5 y	5.6% (CR)	5.6% (CR)

Notes: *Mean; **The interval of each GKRS session was > 2 years; †This is a study on 76 patients but the outcome analyses were performed only for the 44 patients who had follow-up data; ‡Sixteen out of 18 patients completed > 36 months of follow-up.

Abbreviations: AVM, arteriovenous malformation; BS, brainstem; CR, crude rate; GKRS, gamma knife radiosurgery; HoH, history of hemorrhage; m, month(s); ND, not described; y, year(s); VSGKRS, volume-staged gamma knife radiosurgery; w, with; wo, without.

difficult to predict; however, the rate is somewhere between 0% and 40%.^{81–90,91,101} A recent systematic review by Ilyas et al noted that the rates of obliteration, symptomatic RAEs, post-radiosurgical hemorrhage, and mortality were 41.2%, 13.7%, 19.5%, and 7.4%, respectively.⁹⁵ Thus, VSGKRS is a therapeutic modality still undergoing development. Given the scarcity of cases in individual centers, a multi-center study is needed for further evaluation.

Combination Of GKRS And Embolization For Large AVMs

The other option for large AVMs is a combination of neoadjuvant nidus embolization and definitive GKRS. Previous relatively large studies reporting this combination are summarized in Table 3.^{104–113} According to several recent studies, the crude obliteration rates range from 24–72%, and 5-year obliteration rates from 31–60%.^{24,104–118} A recent systematic review found the obliteration rate to be 41.0%, the 3-year hemorrhage rate to be 7.3%, and the RAE rate to be 3.3%¹¹⁹ however, these results might be misleading due to volume discrepancies and how they are defined. First, median/mean volumes in the studies included in this systematic review varied significantly; the smallest was 2.8 mL and the largest 29.5 mL. Second, most of the prior studies used residual AVM volume after embolization as a baseline value,^{104,105,108,109,115,120–122} while others employed the pre-embolization volume,^{107,110–114} and two studies did not describe volume in detail.^{116,117} Since AVM volume significantly affects radiosurgical outcomes, these discrepancies present a major obstacle to interpreting the results.

This combination was initially deemed to be ideal because embolization can reduce the nidus volume, with minimal invasiveness, down to the level at which GKRS could be suitably applied.^{123,124} However, several studies later suggested that this approach might be associated with a reduction in the obliteration rate.^{16,109,114,119,120} This reduction might be attributable to several factors including recanalization of the embolized AVM compartments, increased difficulty in AVM demarcation for radiosurgical planning, and increased angiogenesis after embolization.^{36,37,123,125,126–128} Nevertheless, it would be premature to abandon this combination strategy, given the volume issues discussed above. What we can learn from the relevant studies is that the obliteration rate for post-embolized AVMs might be lower than that for non-embolized AVMs with volumes similar to the residual

volumes of embolized AVMs. Comparing post-embolized AVMs to non-embolized AVMs with volumes similar to the pre-embolized volume of the former would yield different results. Further studies must be designed to ascertain whether the combination therapy is beneficial for larger AVMs, by comparing the overall outcomes of both embolization and GKRS to a GKRS-based strategy without embolization, with adjustment for the pre-intervention volume between the two cohorts.

GKRS For Unruptured AVMs

Therapeutic interventions for unruptured AVMs were not regarded as being controversial until the Randomized trial of Unruptured Brain Arteriovenous malformations (ARUBA study) failed to show any advantages to treatment.¹²⁹ Since then, however, a significant number of concerns about and criticisms of the ARUBA study have been raised.¹³⁰ From the standpoint of GKRS, the short follow-up duration would be the factor most significantly impairing the reliability of the results; a median follow-up of < 3 years is inadequate to see the benefits of GKRS that would not usually preclude the possibility of AVM rupture until obliteration is achieved after a 3–5 year latency period. Another significant issue is the lack of details regarding the treatment arms; the actual outcomes after GKRS were not documented in detail. To date, several gamma knife centers have reported comparison studies between “ARUBA-eligible patients” and the medically-managed patients in the ARUBA study, and obtained more favorable outcomes in GKRS cohorts in the late phase (Table 4).^{131–136} Therefore, GKRS appears to be warranted for small- to medium-sized unruptured AVMs. Nevertheless, the ARUBA study was undoubtedly a turning point in the management of unruptured AVMs in the sense that it underscored the importance of being fully aware of the invasiveness of treatment and its complications when treating asymptomatic AVMs. GKRS for dural arteriovenous fistula

Current Evidence

DAVFs, accounting for 10–15% of intracranial arteriovenous shunt disorders, are acquired arteriovenous shunts involving the dura mater, where arterialized dural sinuses become an obstacle to normal cerebral venous return, eventually resulting in intracranial hemorrhage and/or non-hemorrhagic neurological deficits due to venous hyperemia.^{137–142} Presence of cortical venous drainage (CVD) and prior hemorrhage are well-known risk factors

Table 3 Literature Review On Outcomes Of A Combination Of GKRS And Embolization (Studies With ≥ 25 patients)

Year	Author	N	Material For Embolization	Median Prescription Dose (Gy)	Median Nidus Volume (mL)	Cases With Prior Hemorrhage	Obiteration Rate (As Compared To Non-Embolized Cohort)	Post-GKRS Hemorrhage Rate	Study Design
2017	Miyachi ¹¹¹	73	NBCA (100%)	ND	Pre, 13.8*	59%	CR, 60.3%	CR, 4.1%	Multicenter single arm retrospective analysis
2017	Strauss ¹¹²	35	Onyx (100%)	20	Pre, 12.2*; Post, 1.8*	40%	CR, 51.4%	CR, 2.9%	Single arm retrospective analysis
2016	Huo ¹¹³	162	Onyx (60%), NBCA (37%), silk/coil (2%)	16.0	Pre, 14.3; Post, 10.9	48.1%	CR, 56.8%	1.71%/y	Single arm retrospective analysis
2015	Oermann ¹⁰⁴	242	NBCA (79%), coil (13%), Onyx (9%)	20	Post, 4.6	50%	30.9%/5 y (worse)	2.0%/y	Matched cohort analysis (emboli + GKRS vs GKRS only)
2015	Lee ¹⁰⁵	25	Onyx (100%)	22	Post, 3.5	36%	34.1%/4 y (no difference)	CR, 4%	Matched cohort analysis (emboli + GKRS vs GKRS only)
2015	Xiaochuan ¹⁰⁷	46**	ND (mostly Onyx)	16.3	Pre, 14.1	50%	CR, 28.2%	1.66%/y	Retrospective analysis focusing on target embolization with GKRS
2012	Schwyzler ¹⁰⁸	215	NBCA (66%), coil (11%), silk (2%)	19.6*	Post, 4.7*	42.8%	CR, 33% (worse)	CR, 6.08%	Retrospective comparison between emboli + GKRS vs GKRS only
2012	Kano ¹⁰⁹	120	PVA (17%), NBCA/isobutyl 2-cyanoacrylate (44%), coil (8%), ND (32%)	18	Post, 6.6	53.3%	55%/5 y (worse)	2.7%/y	Matched cohort analysis (emboli + GKRS vs GKRS only)
2000	Miyachi ¹¹⁰	37	NBCA (100%)	ND	Pre, 21.9*; Post, 3.9*	40.5%	CR, 49% (for > 90% occlusion)	CR, 5.4%	Single arm retrospective analysis

Notes: *Mean. **Forty-six out of 86 patients had follow-up data.

Abbreviations: CR, crude rate; GKRS, gamma knife radiosurgery; NBCA, n-butyl cyanoacrylate; ND, not described; Post, post-embolization; Pre, pre-embolization; PVA, polyvinyl alcohol particle; y, year(s).

Table 4 Literature Review On Outcomes Of ARUBA-Eligible Patients (Studies With ≥ 100 patients)

Year	Author	N	Median Follow-Up Period (m)	Median Age At GKRS (y)	Median Nidus Volume (mL)	Obliteration Rate	Stroke Or Death Rate
2019	Karlsson ¹³⁶	1351	60	41	5	61% (CR)	5.8%/2 y (stroke), 1.4%/2 y (death)
2018	Tonetti ¹³⁴	233	100.8	42*	ND	72% (CR)	0.8%/y
2017	Ding ¹³³	232	90.5*	42*	2.1*	72%/5 y	10.3% (CR for stroke or death), 1.0%/y (stroke)
2016	Ding ¹³¹	509	86*	40*	3.0*	75% (CR)	0.9%/y (stroke), 1.0–2.9% (death, depending on whether the unknown causes of death were related to AVM or not)
2016	Hanakita ¹³⁵	240	62	39	4.3	73%/6 y	1.1%/y (stroke)
2013	Pollock ¹³²	174	64	42.5	5.6	69.7% (CR)	10.3%/5 y (stroke or death)

Notes: *Mean.

Abbreviations: ARUBA, A Randomised trial of Unruptured Brain Arteriovenous malformations; CR, crude rate; m = month(s); GKRS, gamma knife radiosurgery; ND, not described; y, year(s).

for future hemorrhage.^{137,138,141,143,144–146} The estimated annual event rates are 7–19% for DAVFs with CVD and/or prior hemorrhage, though the rates range from 0–1.5% in the absence of these aggressive features.^{137,143,147–149} During GKRS, the irradiation target is shunt tissues in the dura mater which can be seen on time-of-flight MRI and DSA. The prescription dose is usually between 18 and 22 Gy in most institutions. Fistula obliteration is achieved in 41–90% of treated patients after a latency period of several months to years (typically 1–3 years), with an acceptable hemorrhage rate below 5% as well as low symptomatic RAE rates ranging from 0–5%.^{150–164} The results of recent studies with significant numbers of study participants (≥ 20) are summarized in Table 5.^{152–155,157,161–165}

Unresolved Issues And Future Tasks

First, no consensus has been reached regarding factors associated with successful obliteration. Knowing those factors would be an important first step to refining appropriate case selection and radiosurgical planning, and to tailoring treatment strategies to individual patients. Several studies have attempted to identify these crucial factors, but to date cavernous sinus location and absence of CVD are the only factors suggested by more than one study.^{152,154,165,166} The inconsistencies among these studies indicate that further investigations are necessary to clarify the relevant issues. Unlike AVM, DAVF is likely to be treated not only with GKRS alone but also in combination with embolization and/or surgery, making it difficult to assess the reasons for failed obliteration after GKRS.

Second, the outcomes of GKRS as a solo treatment remain to be fully elucidated. Due to the latency period in which hemorrhage risk cannot be regarded as negligible, GKRS is generally considered to be an alternative method when endovascular embolization and direct surgery are not feasible or have failed, or for patients with significant medical comorbidities.¹⁴⁴ As such, in almost all published studies focusing on GKRS for DAVFs, a significant number of patients underwent embolization before GKRS or scheduled embolization immediately after GKRS. Nevertheless, GKRS is more advantageous in terms of safety and minimal invasiveness than the other therapeutic modalities; GKRS alone is thus potentially a good therapeutic option when endeavoring to achieve a balance between efficacy and safety. Indeed, Park et al reported a 90% obliteration rate with a 0% hemorrhage rate, suggesting that GKRS might provide acceptable outcomes when used as a solo treatment.¹⁶³ However, their study was based on only 20 patients.

Third, since studies have suggested that cavernous sinus location is associated with fistula obliteration, fistula location may affect radiosurgical outcomes. Taking AVMs as an example, nidus location significantly affects treatment outcomes.^{16,25,41,49,167} To date, however, no study has addressed this issue, probably due to relatively small patient numbers. Starke et al recently reported the first multicenter retrospective analysis of data from 114 patients, approximately half of whom had undergone prior embolization, though they did not show location-specific outcomes, a factor which should be considered in future studies.¹⁶⁵

Table 5 Literature Review Describing Stereotactic Radiosurgery For DAVFs (Studies With ≥ 20 patients)

Year	Author	N	Median Prescription Dose (Gy)	Cases With Embolization	Cases With Prior Hemorrhage	Cases With CVD	Crude Obliteration Rate	Hemorrhage Rate	RAE Rate	Factors Associated With Successful Obliteration	Remarks
2019	Starke ¹⁶⁵	114	Mean, 21.8	47%	24%	52%	68%	0.9%/year	3.5%	Female sex, absence of venous ectasia, CS location	Multicenter study
2018	Tonetti ¹⁶¹	42	20	67%	31%	100%	64%	0.8%/year	/	/	All cases had CVD
2018	Chen ¹⁶²	27*	Mean, 20	63%	44%	63%	63%	3.3%/year	/	None	All cases had high-risk features
2016	Park ¹⁶³	20	Mean, 16.8	0%	5%	60%	90%	0%	5%	/	No cases had prior embolization
2013	Pan ⁵⁰	264	Mean, 17.2	13%	/	45%†	66%	0.8%	0.4%	/	/
2012	Hanakita ¹⁵²	22	20	45%	27%	68%	55%	0%	0%	Absence of CVD, prior hemorrhage, volume < 1.5 mL, Cognard type III/IV	/
2010	Cifarelli ¹⁵⁴	55	21	65%	36%	71%	54%	5.4%	1.8%	Absence of CVD, Borden type I ^{‡‡}	/
2010	Yang ¹⁵³	40	20	30%	18%	50%	73%	2.5%	0%	CS location ^{‡‡}	/
2006	Soderman ¹⁵⁵	49	Mean, 23	17%	39%	69%	68%	4.0%	2.0%	/	/
2001	Friedman ¹⁵⁷	23	18	87%‡	9%	17%	41%§	0%	0%	None	/
1999	Pollock ¹⁵⁸	20	20	65%‡	0%	20%	65%	0%	0%¶	/	CS DAVF only

Notes: *The entire cohort includes 41 patients but follow-up data were available for only 27. †52 of the 115 patients with non-CS DAVFs had CVD. ‡‡Results from univariate analyses; multivariate analysis was not performed. ‡Planned post-radiosurgical embolization was included. §Calculated from data not including patients lacking follow-up angiography (n = 6). ¶One recurrence of visual symptoms was noted.

Abbreviations: CS, cavernous sinus; CVD, cortical venous drainage; DAVF, dural arteriovenous fistula; RAE, radiation-induced adverse event; TS, transverse-sigmoid.

In conclusion, GKRS has the potential to become a first-line therapeutic option for DAVFs. However, its efficacy must be further confirmed with additional studies based on a large number of participants. Due to the scarcity of cases in a single institution, this goal might be achievable only by conducting a multi-institutional investigation with a large combined sample population. At present, a multi-institutional study is ongoing in Japan (JLGK1802, University Medical Information Network Registry No. UMIN000037211).

GKRS For Cavernous Malformation Current Evidence

Brain CM is a low-flow and angiographically-occult vascular lesion, accounting for 10% to 15% of all brain vascular malformations.^{168–170} A CM becomes symptomatic when it bleeds and expands or causes seizures. In general, the hemorrhage rate for those in deep locations (for brainstem, thalamus, and basal ganglia lesions, the hemorrhage rate is 3–10%/year) exceeds that for CM in lobar locations (0–12%/year), and the rate for those with prior hemorrhage (5–23%/year) is higher than that for CM without prior bleeding (0–1%/year).^{171–177} The 5-year risk of additional hemorrhage or neurological decline for those with a prior hemorrhage is high, up to 42% if untreated, though the risk diminishes over time.¹⁷⁸

Asymptomatic CMs are better managed conservatively since the risk of a first-ever intracranial hemorrhage is low and functional impairment from the hemorrhage would be mild; only patients with symptomatic and/or progressive lesions are regarded as good candidates for interventions.^{170,178–180} Surgical resection is recommended for superficial lesions; whereas radiosurgery is considered for those located deep inside the brain, such as lesions in the basal ganglia, thalamus, and brainstem.^{169,170,179}

Before the early 2000s, mainly high radiosurgical doses (≈ 18 Gy) were used, which contributed to a relatively high rate of RAEs.^{181–184} Currently, low doses (≤ 15 Gy) are generally preferred, and provide a level of effectiveness similar to that of higher doses but with a lower risk profile (Table 6).^{181,185–195}

The goal of GKRS is to minimize the risk of bleeding, which can be achieved within an approximately two-year latency period. The short- to mid-term outcomes up to ≈ 5 years are well-known. Recent retrospective studies have shown the post-radiosurgical hemorrhage rates to range

from 3.3–15%/year within two years after GKRS and 0.8–4.7%/year thereafter (Table 2), a remarkable reduction compared to the pre-radiosurgical hemorrhage rates ranging from 20–40%.^{181,185–195} The histopathological responses following GKRS are not yet fully understood. Based on the best of currently available evidence, GKRS induces collagen formation, vessel wall-thickening, thrombus formation, and hyalinization in CM sinusoids, which then develop over the course of several months to a few years.^{196–198} These changes can be accompanied by some areas of neovascularization, which might be responsible for post-radiosurgical hemorrhage and raise the concerns discussed below.¹⁹⁸

Unresolved Issues And Future Tasks

First, the optimal radiosurgical dose for CMs has not as yet been standardized, with the mean prescription doses ranging from 11 and 16 Gy (Table 6).^{181,185–195} Reflecting this, the dose-volume response also has not been clarified. These two issues are rather challenging because, unlike AVMs, there would be little visible or apparent change allowing clinicians to determine whether GKRS is effective. The only measurable therapeutic outcome is the hemorrhage rate.

Second, long-term efficacy has not been adequately examined. It seems that GKRS cannot completely eliminate the hemorrhage risk. To date, three studies have attempted to address this issue,^{186,194,195} of which the one with the longest follow-up (mean, 9.3 years)¹⁸⁶ showed a post-radiosurgical hemorrhage rate for the first 5 years of 1.5–3.3%/year, apparently much better than the natural history documented in a prospective study¹⁷⁸ (the rate of hemorrhage or neurological event; 20%/year during the first year, 12–13%/year during the second to third years, and 5%/year during the fourth to fifth years), while a mild increase up to 4.6%/year was noted after 5 years. These data underscore the importance of conducting further research, with larger patient populations and longer follow-up periods, to define the long-term efficacy of GKS.

Conclusion

GKRS is highly effective for small to medium-sized AVMs. VSGKRS and a combination of embolization and GKRS are currently being developed as therapeutic options for larger AVMs. These approaches require additional evaluation with larger sample sizes and longer follow-up periods. GKRS for DAVF is feasible as a

Table 6 Literature Review Of Recent Studies Describing Stereotactic Radiosurgery For CMs

Year	Author	N	Mean F/U (Month)	Mean Age (Year)	Mean Diameter (mm)	Mean Volume (mL)	Location	Mean Prescription Dose (Gy)	Hemorrhage rate		Rate Of New Neurological Deficits
									Before GKRS	After GKRS	
2018	Park ¹⁸⁶	45	112	37	NA	1.8	BS	13	40%/y	3.3%/y (<2y), 1.5%/y (2–5y), 4.6%/y (>5y)	2.6%
2018	Jacobs ¹⁹⁴	76	NA	42	NA	0.66**	BS	15**	31%/y	4%/y	9%
2018	Sheen ¹⁹⁵	81	79**	39	NA	1.0	Any	14	NA	7.5%	NA
2016	Liu ¹⁸⁷	43	36	42	NA	0.44	BS	12	25%/y	3.9%/y (<2y), 1.9%/y (>2y)	2.3%
2015	Kida ¹⁸⁵	298	68	39	15	N/A	BS, Thal, BGL, others	15	21%/y	7.4%/y (<2y), 2.8%/y (>2y)	6.7%
2012	Lee ¹⁸⁹	49	41	39	32	3.2	BS	11	31%/y	4.3%/y (<2y), 3.6%/y (>2y)	4.1%
2010	Lunsford ¹⁹⁰	103	24–240*	39	NA	1.3**	BS, Thal, BGL, others	16**	33%/y	11%/y (<2y), 1.1%/y (>2y)	14%
2010	Nagy ¹⁹¹	113	48	37	NA	0.34–0.83	BS, Thal, BGL	12	31%/y [†] 2.2%/y	15%/y (<2y) [‡] , 2.4%/y (>2y) [‡] 5.1%/y (<2y) [‡] , 1.3%/y (>2y) [‡]	7.3%
2010	Monaco ¹⁹³	68	62	41	NA	1.2	BS	16	32%/y	8.2%/y (<2y), 1.4%/y (>2y)	12%
2009	Kida ¹⁹²	84	55	38	14	N/A	BS, Thal, BGL	13	NA	9.5%/y (<1y), 4.7%/y (1–2y)	3.2%
2002	Hasegawa ¹⁸¹	82	59	38	NA	1.9	BS, Thal, BGL, others	16	34%/y	12%/y (<2y), 0.76%/y (<2y)	7.3%

Notes: *Detailed data on the median or mean value not provided. **Median. †Results of high-risk group. ‡Results of low-risk group
Abbreviations: BGL, basal ganglia; BS, brainstem; F/U, follow up; GKRS, gamma knife; NA, not assessed; Thal, thalamus.

minimally invasive option but further multicenter studies are needed to both clarify efficacy as a solo treatment modality and confirm factors required for successful obliteration, as well as to examine location-specific outcomes. GKRS for CMs is also feasible for obtaining short- to mid-term prevention of additional hemorrhage. Further long-term follow-up studies are necessary to identify the long-term benefits of GKRS and optimize radiosurgical doses.

Disclosure

The authors report no conflicts of interest in this work.

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