Long-term safety and efficacy of stereotactic radiosurgery for vestibular schwannomas: evaluation of 440 patients more than 10 years after treatment with Gamma Knife surgery

Clinical article

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Object. Little is known about long-term outcomes, including tumor control and adverse radiation effects, in patients harboring vestibular schwannomas (VSs) treated with stereotactic radiosurgery > 10 years previously. The aim of this study was to confirm whether Gamma Knife surgery (GKS) for VSs continues to be safe and effective > 10 years after treatment.

Methods. A total of 440 patients with VS (including neurofibromatosis Type 2) treated with GKS between May 1991 and December 2000 were evaluable. Of these, 347 patients (79%) underwent GKS as an initial treatment and 93 (21%) had undergone prior resection. Three hundred fifty-eight patients (81%) had a solid tumor and 82 (19%) had a cystic tumor. The median tumor volume was 2.8 cm³ and the median marginal dose was 12.8 Gy.

Results. The median follow-up period was 12.5 years. The actuarial 5- and ≥ 10-year progression-free survival was 93% and 92%, respectively. No patient developed treatment failure > 10 years after treatment. According to multivariate analysis, significant factors related to worse progression-free survival included brainstem compression with a deviation of the fourth ventricle (p < 0.0001), marginal dose ≤ 13 Gy (p = 0.01), prior treatment (p = 0.02), and female sex (p = 0.02). Of 287 patients treated at a recent optimum dose of ≤ 13 Gy, 3 (1%) developed facial palsy, including 2 with transient palsy and 1 with persistent palsy after a second GKS, and 3 (1%) developed facial numbness, including 2 with transient and 1 with persistent facial numbness. The actuarial 10-year facial nerve preservation rate was 97% in the high marginal dose group (> 13 Gy) and 100% in the low marginal dose group (≤ 13 Gy). Ten patients (2.3%) developed delayed cyst formation. One patient alone developed malignant transformation, indicating an incidence of 0.3%.

Conclusions. In this study GKS was a safe and effective treatment for the majority of patients followed > 10 years after treatment. Special attention should be paid to cyst formation and malignant transformation as late adverse radiation effects, although they appeared to be rare. However, it is necessary to collect further long-term follow-up data before making conclusions about the long-term safety and efficacy of GKS, especially for young patients with VSs.

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Key Words • **Gamma Knife** • **long-term result** • **stereotactic radiosurgery** • **vestibular schwannoma**

S INCE a VS was first treated with radiosurgery in 1969 (as documented by Hirsch et al.[19] in 1979), more than 40 years have passed. To date, many investigators have reported the safety and effectiveness of radiosurgery for VSs during the short to medium term.[8–10,16,]

Abbreviations used in this paper: GKS = Gamma Knife surgery; GR = Gardner-Robertson; HB = House-Brackmann; NF2 = neurofibromatosis Type 2; PFS = progression-free survival; SRS = stereotactic radiosurgery; VS = vestibular schwannoma.

[22–24,28,36,38,40,41,50,51] Consequently, SRS is currently the most common treatment for small- to medium-sized VSs, resulting in good tumor control and functional outcomes. However, because the majority of VSs are histologically benign, it is mandatory to clarify the true long-term results, especially if radiosurgery is applied in young patients. At present, there is little information regarding long-term tumor control > 10 years after radiosurgery[18,25,43] as well as the true incidence of late adverse effects of radiation such as delayed cyst formation, intratumoral hemorrhage,

malignant transformation, and secondary neoplasms. Although to our knowledge the risks of late complications are predicted to be extremely low, the long-term safety and efficacy of radiosurgery should be verified. Otherwise, SRS is not justified for young patients with benign tumors such as VSs. Accordingly, we retrospectively evaluated long-term tumor control and adverse radiation effects in our > 20 years of experience with GKS for VS. These results should contribute to decision-making strategies for younger patients with VSs.

Methods

Patient Characteristics

Between May 1991 and December 2000, 451 consecutive patients harboring VSs including NF2 were treated with GKS in Komaki City Hospital. Eleven patients were lost to follow-up; therefore, a total of 440 patients were assessed. Patient characteristics are shown in Table 1. Three hundred forty-seven patients (79%) underwent GKS as an initial treatment, and the other 93 patients (21%) had experienced prior resection. Thirteen patients (3%) had NF2. Hearing and facial function were evaluated on the basis of the GR classification[11] and HB grading,[20] respectively. Hearing and facial function at the time of GKS are shown in Table 2.

Tumor Classification

All tumors were classified as solid or cystic; the latter included mixed tumors with cystic components. Of 440 patients, 358 (81%) had solid tumors, and 82 (19%) had cystic tumors. Additionally, all tumors were classified into 4 categories depending on the location and the brainstem compression, as follows: Type A, intracanalicular tumor (43 patients [10%]); Type B, cerebellopontine angle tumor without brainstem compression (238 patients [54%]); Type C, tumor compressing the brainstem with no

TABLE 1: Characteristics in 440 patients with VSs*

Variable	No. of Pts (%)
sex	
M	175 (40)
F	265 (60)
age	
range	7–86 yrs
median	55 yrs
side	
lt	222 (50)
rt	218 (50)
no. of prior ops	
0	347 (79)
1	76 (17)
2	13 (3)
3	4 (1)
NF2	13 (3)

* Pts = patients.

TABLE 2: Preradiosurgical hearing and facial function in 440 patients with VSs*

Classification	No. w/ Initial Tx (%)	No. w/ Secondary Tx (%)	Total (%)
GR class			
I	43 (12)	2 (2)	45 (10)
II	92 (27)	0 (0)	92 (21)
III	134 (39)	13 (14)	147 (34)
IV	39 (11)	11 (12)	50 (11)
V	37 (11)	67 (72)	104 (24)
total†	345	93	438
HB grade			
I	327 (94)	43 (46)	370 (84)
II	13 (4)	22 (24)	35 (8)
III	5 (1)	8 (9)	13 (3)
IV	2 (1)	14 (15)	16 (4)
V	0 (0)	6 (6)	6 (1)
VI	0 (0)	0 (0)	0 (0)
total	347	93	440

* Tx = treatment.
† Pretreatment hearing class was unknown in 2 patients at initial treatment.

deviation of the fourth ventricle (92 patients [21%]); and Type D, tumor with a deviation of the fourth ventricle (67 patients [15%]) (Fig. 1).

Radiosurgical Techniques

The GKS procedure was performed with the aid of the Leksell model G stereotactic frame (Elekta Instruments). The frame was applied after mild sedation and
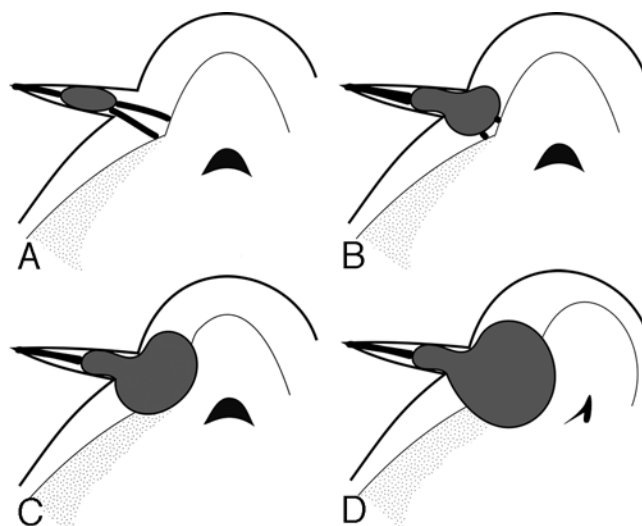

FIG. 1. Schematic drawings showing tumor classification depending on the location and brainstem compression. **A:** Type A—intracanalicular tumor. **B:** Type B—a cerebellopontine angle tumor without brainstem compression. **C:** Type C—tumor compressing the brainstem with no deviation of the fourth ventricle. **D:** Type D—tumor with a deviation of the fourth ventricle.

local anesthesia had been administered. After frame application, all patients underwent MRI studies; axial and coronal T1-weighted images with contrast enhancement were used for dose planning. All patient treatment was planned with the KULA system until 1996, and thereafter GammaPlan software was used. After dose planning, GKS was performed using the Leksell Gamma Knife, model B (software and Gamma Knife obtained from Elekta Instruments). The maximum and marginal doses varied from 13 to 36 Gy (median 25 Gy) and from 10 to 18 Gy (median 12.8 Gy), respectively. The isodose line for the tumor margin varied from 40% to 95% (median 50%). The number of isocenters varied from 1 to 12 (median 3). The tumor volume varied from 0.07 to 36.7 cm³ (median 2.8 cm³).

Follow-Up Method

Clinical follow-up data were obtained from either the patient or the referring doctor if the patient lived at a distance from our institution. When necessary the patients were contacted, and provided a questionnaire or telephone interview to update their outcomes for the purposes of this study. Radiographic studies were requested at 3-month intervals for the 1st year after GKS, at 6-month intervals for the next 2 years, and then annually. Tumor enlargement or regression was defined as a change of ± 2 mm in one direction, measured with calipers.

Statistical Analysis

The PFS was calculated using the product limit method of Kaplan and Meier. When calculating PFS, treatment failure was defined as tumor enlargement or radiation-induced peritumoral edema requiring resection. To analyze factors that correlated with PFS, the following were assessed: sex (male vs female), age (< 65 vs ≥ 65 years), prior treatment (no vs yes), tumor nature (cyst vs solid), tumor type (Type A, B, or C vs Type D), tumor volume (< 10 cm³ vs ≥ 10 cm³), maximum dose (≤ 26 Gy vs > 26 Gy), marginal dose (≤ 13 Gy vs > 13 Gy), and number of isocenters (< 5 vs ≥ 5). Factors affecting PFS were assessed with the log-rank test and the Cox proportional hazards model. A final multivariate analysis was calculated using a stepwise backward elimination. Probability values < 0.05 were considered statistically significant.

Results

At the last follow-up, 402 patients were alive and 38 were dead. Four patients with tumor volumes of 4, 16, 18, and 21 cm³ died of VSs 10–79 months after GKS. The median follow-up period was 12.5 years. Three hundred eleven patients (71%) were followed for > 10 years, and 115 of these 311 patients (26% of the study cohort of 440) were clinically followed for > 15 years.

Tumor Control

Follow-up radiological studies were unavailable in 13 patients. Therefore, these patients were excluded from the calculation of PFS with the Kaplan-Meier method, although these patients had not experienced any additional

treatments for VSs. One hundred eighty-eight patients (43%) and 53 patients (12%) had follow-up images at > 10 years and > 15 years after GKS, respectively. On the last follow-up image, 3 patients (1%) had a complete remission, 246 (58%) had a partial remission, 147 (34%) had stable tumor, and 31 (7%) had treatment failure. Twenty-three patients developed treatment failure within 3 years after GKS, whereas 8 developed treatment failure > 3 years after GKS. No patient experienced treatment failure > 10 years after GKS. All patients with NF2 had good tumor control at the last follow-up evaluation. The actuarial 5-year and ≥ 10-year PFS rates were 93% and 92%, respectively (Fig. 2).

Factors Associated With PFS

In univariate analysis, tumor volume (p < 0.0001), tumor type (p < 0.0001), number of isocenters (p = 0.018), prior treatment (p = 0.02), marginal dose (p = 0.03), and sex (p = 0.046) affected PFS significantly. In multivariate analysis, tumor type (p < 0.0001), marginal dose (p = 0.01), prior treatment (p = 0.02), and sex (p = 0.02) remained significant (Table 3). No other factors were significantly associated with PFS. Based on tumor type, the actuarial ≥ 10-year PFS was 100% in Type A, 95% in Type B, 92% in Type C, and 76% in Type D tumors. The Type D tumors were significantly worse for tumor control compared with Types A, B, and C as a group (p < 0.0001, Fig. 3 upper). Type D tumors were significantly worse for tumor control compared with Type C tumors alone (p = 0.004), whereas there was no significant difference between Type B and Type C tumors (p = 0.33).

Based on tumor volume, the actuarial 10-year PFS was 94% in small tumors (< 10 cm³), compared with 77% in large tumors (≥ 10 cm³) (p < 0.0001, Fig. 3 lower). Even when tumor volume was analyzed with continuous variables, larger tumors were significantly worse for tumor control, with a hazard ratio of 1.122 per cm³ (p < 0.0001, 95% CI 1.079–1.166 per cm³). Tumor nature did not affect PFS significantly (p = 0.58). Marginal dose > 13 Gy significantly contributed to good tumor control (p = 0.03). However, if limited to the 363 patients who had small tumors of < 10 cm³ in volume, the actuarial 10-year PFS
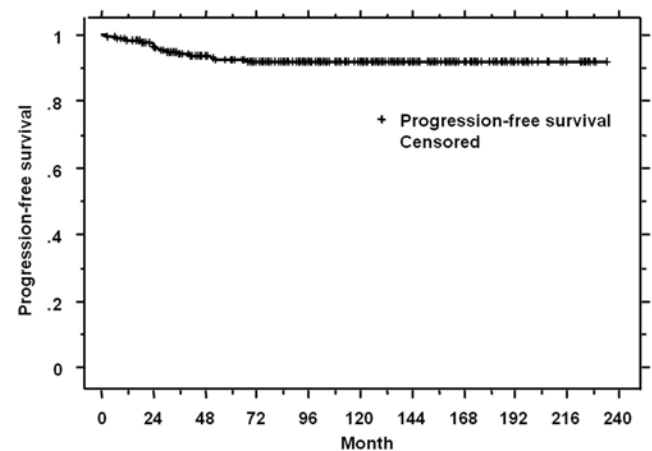

Fig. 2. Kaplan-Meier curve demonstrating PFS in 427 patients in whom follow-up radiological studies were available.

TABLE 3: Factors affecting PFS in 427 patients with VSs*

Factor	No. of Pts	% w/ PFS		p Value	
		5 Yrs	10 Yrs	Univariate	Multivariate
sex					
M	168	95	95	0.046†	0.021†
F	259	91	89		
age in yrs					
<65	331	92	92	0.86	NT
≥65	96	94	93		
prior Tx					
no	334	95	93	0.021†	0.015†
yes	93	86	86		
nature of lesion					
cyst	80	90	90	0.58	NT
solid	347	93	92		
tumor type					
A, B, or C	361	95	95	<0.0001†	<0.0001†
D	66	78	76		
tumor vol					
<10 cm³	363	95	94	<0.0001†	0.17
≥10 cm³	64	79	77		
max dose					
≤26 Gy	282	94	93	0.20	NT
>26 Gy	145	90	90		
marginal dose					
≤13 Gy	287	91	90	0.032†	0.011†
>13 Gy	140	96	96		
no. of isocenters					
<5	274	95	94	0.018†	0.91
≥5	153	88	88		

* Thirteen patients in whom radiological images were not available were excluded. Abbreviations: max = maximum; NT = not tested.
† Significant difference at p < 0.05.

was 96% in the high-dose group (123 patients) and 94% in the low-dose group (240 patients), demonstrating that a reduced marginal dose of 12–13 Gy did not affect the long-term PFS significantly (p = 0.62).

Salvage Treatment

Thirty-six patients (8%) underwent further treatment for VSs. The mean interval to the second treatment was 31 months. Thirty patients underwent craniotomy as a second treatment 3–68 months after GKS. Of these, 7 patients underwent craniotomy on the advice of their referring doctors in spite of unchanged tumor volume or slight tumor expansion, although the biological process would have probably led to later tumor regression. One had craniotomy for treatment of intratumoral hemorrhage after tumor regression. Six patients underwent a second GKS with a mean marginal dose of 11 Gy 24–70 months after the first GKS. Of these, 3 patients achieved tumor shrinkage with no complications, and the other 3 eventually underwent craniotomy. The actuarial 5-year and ≥

10-year additional treatment-free survival was 92% and 91%, respectively. Twenty-five patients (6%) developed hydrocephalus requiring a ventriculoperitoneal shunt between 7 days and 47 months after GKS (mean tumor volume 10.7 cm³, range 0.7–36.7 cm³). Of these, 8 patients developed hydrocephalus with treatment failure.

Functional Outcomes and Complications

Detailed long-term hearing results after GKS were documented in our previous paper.[17] Briefly, in the evaluation of 117 patients in that earlier paper who retained serviceable hearing of GR Class I or II at the time of GKS, the actuarial 3-, 5-, and 8-year hearing preservation rates were 55%, 43%, and 34%, respectively. Based on marginal dose group, the actuarial 3- and 5-year hearing preservation rates were 58% and 46%, respectively, in patients treated at a marginal dose of ≤ 13 Gy and 37% and 19%, respectively, in patients treated at a marginal dose of > 13 Gy (p = 0.37). Based on GR classification, the actuarial 3- and 5-year hearing preservation rates were 71% and 64%,
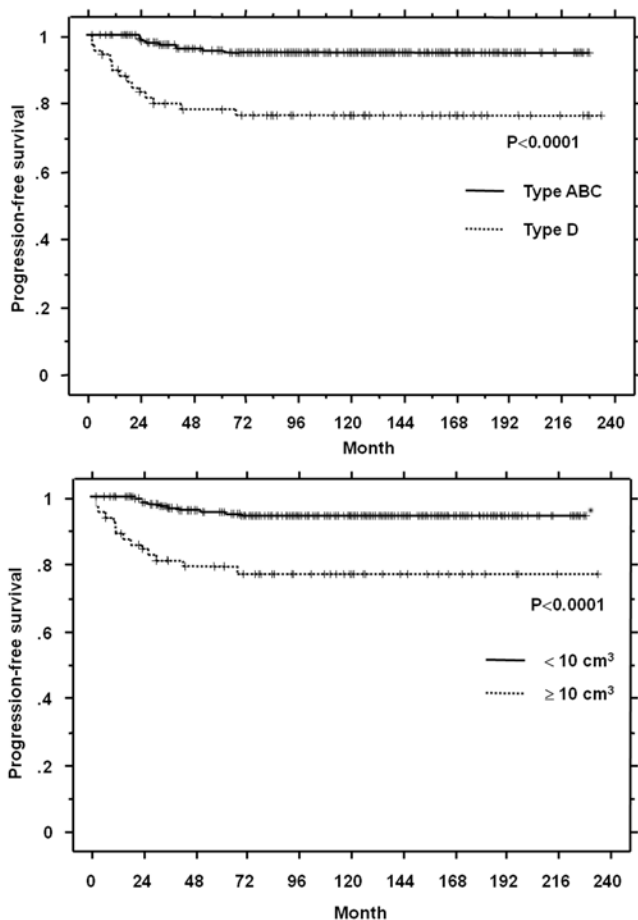
FIG. 3. A comparison of Kaplan-Meier curves showing PFS between patients with Types A, B, or C and Type D tumors **(upper)**, and between patients with tumors < 10 cm^3 and ≥ 10 cm^3 **(lower)**.

respectively, in patients with pre-GKS GR Class I hearing and 40% and 24%, respectively, in patients with Class II hearing (p = 0.0003). Compared with pre-GKS pure tone average, a decline of approximately 20 dB was found at 3 to 5 years after GKS on the tumor side, whereas hearing function was almost unchanged even 10 years later on the contralateral side.

Based on marginal dose group, the risks of facial palsy, facial numbness, and facial spasm are shown in Table 4. Among the patients treated at a marginal dose of > 13 Gy, 5 developed persistent facial palsy (including HB Grade II in 3 patients, Grade III in 1, and unknown in 1) and 2 developed transient facial palsy. Of patients treated at a recent optimum dose of ≤ 13 Gy, only 2 developed transient facial palsy—although 1 had persistent palsy (HB Grade IV) after a second GKS. The actuarial 10-year facial nerve preservation rate was 97% in the high-dose group (> 13 Gy), whereas it was 100% in the low-dose group (≤ 13 Gy), excluding the patient who developed persistent facial palsy after a second GKS. Three patients developed trigeminal neuralgia. As a result, 2 required craniotomy at 32 and 41 months, respectively, and another had GKS for neuralgia at 57 months. One patient's preexisting trigeminal neuralgia resolved at 12 months. Three patients had peritumoral edema causing a bedridden state. One patient had intratumoral hemorrhage. One patient experienced rupture of a vertebral artery aneurysm originating at the posterior inferior cerebellar artery, although the relationship to GKS was unknown.

Delayed Cyst Formation

Delayed cyst formation was found in 10 patients (2.3%) at a mean period of 71 months after GKS (range 30–142 months). Of these, 3 patients required further treatment at 33, 53, and 70 months after GKS, including craniotomy in 2 and a second GKS session followed by craniotomy in 1 patient. The other 7 patients needed no additional treatments, because their cysts were stable with no neurological deterioration, or collapsed naturally.

Malignant Transformation

During a total of 5098 patient-years of follow-up, 1 patient with unilateral VS developed a malignant transformation as described in our previous paper.[16] Briefly, the patient was a 56-year-old woman with a VS 4 cm^3 in volume that was treated at a marginal dose of 12.7 Gy. The tumor was stable at 48 months, but 4 months later the patient required craniotomy because of sudden tumor enlargement, although histological investigation still demonstrated a benign tumor. After that, however, the tu-

TABLE 4: Adverse radiation effects based on marginal dose

Effect	Marginal Dose					
	>13 Gy (143 pts)			≤13 Gy (287 pts)		
	Persistent	Transient	%	Persistent	Transient	%
facial palsy	5	2	4.9	1*	2	1.0
HB grade						
II	3					
III	1					
IV				1		
unknown	1					
facial numbness	3	2	3.5	1	2	1.0
facial spasm	0	2	1.4	0	5	1.7

* After second GKS.

mor grew rapidly, requiring repeat craniotomy 66 months after GKS, and showing malignant change. The patient eventually died at 79 months in spite of 5 craniotomies, 2 GKS treatments, and 1 linear accelerator radiosurgery. There was no tumorigenesis in any other case. No patient with NF2 experienced malignant change. The overall malignant transformation rate in this study was 0.3%, calculated by the Kaplan-Meier method. The annual incidence of malignant change was 0.02%.

Discussion

Long-Term Tumor Control

In recent decades, numerous published articles have shown that GKS is effective for tumor control in patients harboring small- to medium-sized VSs.[8–10,16,22–24,28,36,38,40,41,50,51] Additionally, GKS has been a reasonable alternative to resection, especially for older patients or those with medical comorbidities. Because VSs are benign, to truly recommend GKS to young patients, it should first be confirmed that radiosurgery will continue to be safe and effective all their life. In this study, a total of 440 patients harboring VSs treated with GKS > 10 years previously at our institution (since 1991) were evaluated to clarify long-term tumor control, with a median follow-up period of 12.5 years.

To our knowledge, this is one of the largest series of VSs treated using SRS ever studied, with the longest follow-up data. The actuarial 5-year and ≥ 10-year PFS were 93% and 92%, respectively, as calculated with the Kaplan-Meier method. If limited to tumors < 10 cm³, the 5- and 10-year PFS values increased to 95% and 94%, respectively. No patient experienced treatment failure > 10 years after GKS. Note that one-third of the patients were treated at a high marginal dose of > 13 Gy despite the recently reduced optimum marginal dose of ≤ 13 Gy to avoid hearing deterioration or facial palsy. The actuarial ≥ 10-year PFS in patients treated at a lower marginal dose of ≤ 13 Gy was 90%, compared with 96% in those treated at a higher dose. Although a higher dose tended to result in better tumor control, it should be considered that this result was influenced by the fact that larger tumors were usually treated at lower marginal doses. In a limited number of patients with small tumors (< 10 cm³), the actuarial 10-year PFS was 94% in 240 patients treated at lower doses (≤ 13 Gy), compared with 96% in 123 patients treated at higher doses (> 13 Gy), demonstrating that reduced marginal dose was not significantly related to worse long-term PFS (p = 0.62).

In general, it has been assumed by most neurosurgeons that VSs with brainstem compression should first be removed, but are not suitable for radiosurgery because of a high risk of peritumoral edema after treatment. However, our results did not demonstrate that mild brainstem compression (Type C) caused treatment failure significantly. The most important factor causing treatment failure was whether a fourth ventricle deviation (Type D) existed on MRI studies before treatment, because even slight tumor expansion can cause severe gait disturbance requiring craniotomy. Patients with prior surgeries significantly developed treatment failure, particularly in patients who had previously undergone ≥ 2 surgeries. In this study, 4 (25%) of 16 patients who underwent ≥ 2 prior surgeries eventually developed treatment failure, indicating that recurrent tumors tend to be more aggressive. Also, female patients were more likely to develop treatment failure, but the reason was not evident. With respect to tumor nature (cyst vs solid), although most neurosurgeons tend to prefer microsurgery to radiosurgery for the treatment of cystic tumors because of a risk of rapid cyst expansion after radiosurgery, the tumor's nature did not affect PFS significantly in our study.

Delayed Cyst Formation

Delayed cyst formation is one of the most common late adverse radiation effects. In this study, 10 patients developed delayed cyst formation between 30 and 142 months after GKS. Of these, only 3 patients underwent salvage treatment. The others did not require any additional treatments because the cysts were stable in size with no neurological deficits, or they naturally collapsed. The mean original tumor volume was 8.5 cm³ (range 1.7–25.1 cm³), and these tumors were treated at a mean marginal dose of 12.8 Gy (range 12–14 Gy). Nine patients originally had solid tumors and one had a cystic tumor. Relatively large solid tumors were likely to develop delayed cyst formation in our cases, regardless of radiation doses. Delayed cyst formation was classified into 2 progressive patterns of intratumoral and extratumoral cyst formation.

Although the mechanism of cyst formation is still unclear, it is postulated that intratumoral cyst formation is caused by radiation-induced repeat microbleeding or increased vascular permeability.[37,39] On the other hand, an extratumoral cyst appears to be CSF trapped by adhesion of irradiated tumors, and it is postulated that the cyst expands due to an osmotic effect. Of the 10 patients who developed delayed cyst formation, 6 had intratumoral and 4 had extratumoral cyst. Three of the 6 patients with intratumoral cyst formation eventually underwent resection. None of the patients with extratumoral cyst formation required any additional treatments. Similarly, Murakami et al.[34] reported that in 5 (1.1%) of 449 patients with VS treated with GKS, 3 had delayed newly developed cysts and 2 had enlarged preexisting cysts. Of these, 3 patients developed intratumoral cyst and 2 developed extratumoral cyst. Interestingly, all of the tumors were classified into Koos Grade IV with a mean target volume of 11.3 cm³, and eventually required salvage microsurgery.

Those authors found that intratumoral cysts contained hemorrhage or necrotic debris, whereas extratumoral cysts were composed of thin and semitransparent membrane with xanthochromic fluid, and there were no tumor cells on the cyst wall. In 1 patient with intratumoral cyst formation, cavernous angioma was found within the solid component adjacent to the cyst. It is unknown whether the development of delayed intratumoral cyst is associated with repeat hemorrhage caused by de novo cavernous angiomas after radiation or by the coexistence of angiomas within VSs at onset.[7,35]

Malignant Transformation

Until now, malignant transformation of benign VSs

after SRS was believed to be extremely rare. Recently, however, a number of articles have been published documenting malignant transformation of VSs following radiosurgery.[1,2,5,6,15,16,21,27,30,32,45–47,49,53] Among 440 patients with VS in this study, who had a relatively long median follow-up duration of 12.5 years, only 1 patient developed malignant transformation, indicating an incidence of 0.3%. In fact, it was not evident whether GKS directly affected malignant transformation in our case because there was no histological confirmation of the tumor type before GKS.

Although primary malignant VSs are extremely rare, there may be a possibility of a natural course unrelated to radiation, as reported by several authors.[3,12–14,26,31,33,48] All previously published cases of VSs with malignant transformation or secondary neoplasms after radiosurgery are shown in Table 5. Among them 4 cases were reported from Japan. The case reported by Hanabusa et al.[15] had malignant transformation only 6 months after GKS. In this case it may have been possible that the atypical or malignant component existed before GKS, because there was an insufficient latency interval to develop radiation-induced malignancy.

According to data accumulated by the Leksell Gamma Knife Society, between 1991 and the end of 2010 an estimated 10,514 VSs were treated with GKS at 56 units in Japan. If limited to Japanese cases to increase the reliability of calculation, the estimated incidence of malignant transformation or secondary neoplasms after GKS is 0.03%, excluding the case reported by Hanabusa et al.[15]

Furthermore, if 3423 recent cases treated between 2007 and 2010 are excluded from the calculation due to an insufficient latency interval to develop radiation-induced malignancy, the estimated incidence is 0.04%. Even if the calculation included the case reported by Hanabusa et al., the incidence ranged from 0.04% to 0.06%. Although these figures may be underestimated because of the lack of publication of a few radiation-induced malignancies, the incidence appeared to be < 0.1% at worst. Importantly, this fatal risk was lower than one-fifth of the postoperative mortality rate of 0.5% (22 of 4886 patients) reported in the analysis of VS treated with microsurgery at a total of 374 hospitals in the US between 1994 and 2003,[29] or 0.6% (25 of 3969 patients) reported in a review of 15 microsurgical studies.[52] Also, Samii and Matthies[44] reported a postoperative mortality rate of 1.1% in their large microsurgical series of 1000 VSs treated between 1978 and 1993.

Considering these surgical results, the estimated risk of malignant transformation after GKS would be acceptable. Besides that, it is not even evident whether this fatal risk is really higher than the incidence of malignancy at onset or in the natural course of the disease. According to a report on radiotherapy in childhood for tinea capitis in Israel,[42] the 30-year cumulative risk of secondary brain tumors was 0.8%, with a mean dose to the neural tissue of 1.5 Gy. On the other hand, a report on radiotherapy for pituitary adenomas demonstrated that the 20-year cumulative risk of secondary brain tumors was 1.9% at a median dose of 45 Gy.[4] At the moment, the estimated risk after

TABLE 5: Literature review of radiation-induced malignancies in patients harboring VSs treated with radiosurgery*

Authors & Year	Age (yrs), Sex	NF2	Prior Op	Tx Method	Target Vol	Max/Marginal Dose (Gy)	Latency Period (yrs)	Final Histological Findings
Comey et al., 1998	44, M	no	no	GKS	largest diam 2.7 cm	30/14.4	5	Triton tumor
Thomsen et al., 2000	19, F	yes	yes on contralat side	GKS	1.9 cm³	20/12	6	meningosarcoma
Hanabusa et al., 2001†	57, F	no	yes	GKS	3.4 cm³	30/15	0.5	MPNST
Shamisa et al., 2001	57, F	no	no	GKS	8.6 cm³	27.5/11	7.5	GBM in temporal lobe
Bari et al., 2002	28, F	yes	no	GKS	3.9 cm³	NA/15	4	MPNST
Shin et al., 2002†	26, F	no	yes	GKS	NA	34/17	6	MPNST
McEvoy & Kitchen, 2003	22, M	yes	yes on contralat side	GKS	NA	NA/15	3	no histology (rapid growth)
Hasegawa et al., 2005†	56, F	no	no	GKS	4.0 cm³	23/12.7	5	MPNST
Akamatsu et al., 2010†	67, F	no	yes	GKS	5.1 cm³	24.4/12	8	MPNST
Demetriades et al., 2010	27, M	no	yes	GKS	NA	30/15	10	MPNST
Lee et al., 2010	46, F	no	no	GKS	16.7 cm³	21/12	6	MPNST
Yang et al., 2010	74, M	no	yes	SRS	NA	15.6/12.5	6	HG undiff sarcoma
Husseini et al., 2011	15, M	yes	no	GKS	largest diam 2.2 cm	27/13.5	5	MPNST
Schmitt et al., 2011	51, M	no	no	GKS	19.1 cm³	30/12	7	HG undiff sarcoma
Milligan et al., 2012	59, M	no	NA	GKS	NA	NA	7	pleomorphic sarcoma

* Diam = diameter; GBM = glioblastoma multiforme; HG = high grade; MPNST = malignant peripheral nerve sheath tumor; NA = not available; undiff = undifferentiated.
† Japanese case.

GKS seems to be much lower than that after conventional fractionated radiotherapy, but the duration of follow-up would still be too short to compare with the reports of radiotherapy. Although this fatal risk is extremely low, every patient should be informed of the possibility of this complication before GKS. Because radiation-induced malignancy takes place after a sufficient latency period (usually ≥ 5 years for radiosurgery), it becomes most important to collect further long-term follow-up data and elucidate the true incidence. Otherwise, even if SRS is superior to resection in terms of tumor control and functional outcomes on the short to middle term, SRS would not be truly acceptable for younger patients.

Conclusions

In this study we found that GKS was a safe and effective treatment for VSs in selected patients during a long follow-up period of approximately 10–15 years. No patient experienced treatment failure > 10 years after GKS. In patients who had large VSs compressing the brainstem with a deviation of the fourth ventricle, resection should be recommended first, followed by GKS if necessary. Cyst formation and malignant transformation should be taken into consideration as late adverse radiation effects, although they appear to be rare. Further long-term follow-up is essential to elucidate the true incidences of delayed adverse radiation effects.

Disclosure

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