Long-term results of Gamma Knife surgery for uveal melanomas

Clinical article

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Object. Gamma Knife surgery (GKS) is currently believed to be a safe and minimally invasive modality in the treatment of uveal melanomas. It could be used as an alternative treatment to enucleation, preserving the eyeball as well as visual function. The authors report their experiences with GKS for uveal melanomas for the period from February 1998 to December 2006.

Methods. Twenty-two patients with uveal melanoma were enrolled in this study. The population consisted of 12 men and 10 women with a mean age of 53.4 years (range 24–79 years). The mean tumor volume was 877 mm³, and the mean margin dose was 45.6 Gy. The median follow-up period was 67 months (range 3–126 months). All of the patients had received a diagnosis and referral from an ophthalmology clinic; the patients underwent a preoperative orbital examination that included MRI.

Results. Tumor regression was achieved in 20 patients (90.9%), whereas tumor progression was observed in 2 patients (9.1%) 3 years after GKS. The cumulative 1-year and 2-year mean rates of tumor thickness reduction were 18.8% and 42.8%, respectively. The mean rate of tumor volume reduction was 63.7%. The rate of eye retention 5 years after radiosurgery was 77.3% (17 of 22 patients). Overall visual acuity was reduced after GKS in all patients; 14 patients (63.6%) displayed preserved visual function better than hand-movement perception. The most frequent side effect was cataract, which was detected in 9 patients (40.9%); this was followed in frequency by radiation-induced retinopathy in 5 patients (22.7%).

Conclusions. Gamma Knife surgery provides excellent local control of uveal melanomas with a decrease in volume over time. This procedure not only preserves the eyeball and its potential visual function, but also decreases the potential for hematological dissemination and achieves sufficient local tumor control with a gradual reduction in volume.

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KEY WORDS • uveal melanoma • Gamma Knife • stereotactic radiosurgery

UVEAL melanoma is the most common form of primary intraocular malignancy in adults, with an incidence of 0.61 per 100,000 person-years in whites and 0.05 per 100,000 person-years in African-Americans.^{14,25} Several therapeutic options are available, including resection or enucleation, brachytherapy, and stereotactic irradiation. Despite the range of treatment modalities, the prognosis of this disease still remains discouraging. Whereas traditionally, enucleation has long been the traditional treatment of uveal melanomas, GKS is now believed to be a safe and minimally invasive treatment modality for these lesions. Gamma Knife surgery can preserve the eyeball and visual acuity on one side,

even if it is impossible to preserve it on the other side. The purpose of the present study was to describe our treatment protocol and evaluate the results of GKS in 22 patients treated for uveal melanoma between February 1998 and December 2006.

Methods

Patient Characteristics

We retrospectively reviewed the medical records of 22 patients with uveal melanoma who consecutively underwent GKS between February 1998 and December 2006. The patient population was composed of 12 men and 10 women ranging in age from 24 to 79 years (mean age 53.4 years). The mean tumor volume in these patients was 877 mm³ (range 101.1–5828.6 mm³), and preopera-

Abbreviation used in this paper: GKS = Gamma Knife surgery.

tive visual acuity, determined using the Snellen chart, was between 0.05 and 1.2. The median follow-up period in this population was 67 months (range 3–126 months). The locations of the tumors included anterior to the equator in 8 patients, posterior to the equator in 8 patients, and on both sides of the equator or throughout the whole eye in 6 patients (Table 1).

The diagnosis of uveal melanoma was based on pathological confirmation of the lesion through incisional biopsy in 10 patients (45.5%). In 12 patients the diagnosis was based on imaging and fundoscopic findings without biopsy. All patients had received their diagnosis and referral from ophthalmology clinics, and all had undergone an orbital examination preoperatively. Before GKS, we measured the tumor thickness and the approximate tumor volume.

All patients were examined by an ophthalmologist regularly after GKS, and MRI examinations were performed at regular intervals. Local disease control was defined as freedom from tumor progression and was measured using MRI. The imaging protocol for the treatment plan specified Gd-enhanced MRI using the fat suppression technique as the preferred method. Gadolinium enhancement enables delineation of the tumor from subretinal fluid, hemorrhage, retinal detachment, and choroidal hemangioma. In MRI, the border of the tumor shows a hyperintensity compared to vitreous humor on Gd-enhanced T1-weighted images; on T2-weighted images it displays a slight hypointensity.

Surgical Fixation of the Eye

For successful radiosurgery for uveal melanomas, complete immobilization of the eyeball is considered very important. This can be achieved by a retrobulbar injection of 2% xylocaine followed by transconjunctival fixation of the four rectus muscles using 5–0 silk. Following this, conjunctival flaps are sutured to the upper or lower eyelid and then ophthalmic ointment is applied to the opened eye (Fig. 1).

Treatment Planning

Before September 1999, we used the KULA dose-planning program (initially version 5.4 and later upgraded) to treat patients; after that date, we used the GammaPlan system (version 5.30, Elekta AB). Before October 2004, we used Leksell Gamma Knife model B; thereafter, we used the model C (Elekta AB). After we had upgraded to model C, we were able to use a larger number of small collimators, and it was easier to employ the plugging technique against vital structures. When treating a uveal melanoma, the aim is to surround the tumor with a high isodose. Isodoses in the range of 50% to 97% were used to maximize the falloff of the radiation dose outside the target. The prescribed dose to the tumor margin ranged between 20 to 67.5 Gy and the mean dose was 45.6 Gy. In 19 patients one isocenter was used, and in the other 3 patients two isocenters were used.

Measurements of Tumor Volume and Temporal Changes in Volume

Most of the uveal melanomas had an ellipsoid shape,

TABLE 1: Characteristics in 22 patients with malignant uveal melanomas

Characteristic	Value
sex—no. of patients (%)	
male	12 (54.5)
female	10 (45.5)
mean age in yrs (range)	53.4 (24–79)
mean tumor vol in mm ³ (range)	877 (101.1–5828.6)
tumor location—no. of lesions (%)	
anterior to equator	8 (36.4)
posterior to equator	8 (36.4)
both sides of equator	6 (27.3)
laterality—no. of lesions (%)	
rt	13 (59.1)
lt	9 (40.9)
mean dose (Gy) directed at tumor margin (range)	45.6 (20–67.5)
% isodose (range)	76.3 (50–97)
median follow-up in mos (range)	67 (3–126)

and we measured their volumes using the following formula: volume = $(4/3)(\pi abc)$, where $a = \frac{1}{2}$ long axis, $b = \frac{1}{2}$ short axis, and $c = \frac{1}{2}$ height). This method had limitations in that it was difficult to measure the exact size of the tumor using MRI, and sometimes the tumor shape was not in the form of an ideal ellipsoid, making it difficult to calculate the exact tumor volume. However, we were able to calculate the approximate tumor volume as well as volume changes as time passed.

Statistical Analysis

To evaluate the complications and side effects following GKS, the development of secondary glaucoma, cataract, retinal detachment, and radiation-induced retinopathy after GKS was studied as a function of the prescribed margin dose, tumor localization, and total volume of the prescribed isodose. To determine the statistical significance of these factors, the chi-square test or the Fisher exact test (when the expected value was < 5) was used. The variable was considered significant when the probability value was less than 0.05.

Four different variables were proposed as potential factors influencing regression of the tumor after irradiation of a uveal melanoma using GKS. These factors were patient sex and age, tumor volume, and prescribed margin dose.

Multivariate analyses were performed using the Cox proportional hazards model. Variables with significant probability values ($p < 0.05$) were considered possible factors affecting tumor regression, eye retention, or overall survival. Overall survival and eye retention after GKS were also analyzed using Kaplan-Meier statistics. All statistical analyses in this study were performed using the statistical software package SPSS (version 18, IBM).

Fig. 1. Photograph showing the conjunctival flap suture after fixation of the rectus muscles.

Results

Rate of Eye Retention

Five treated eyes had to be enucleated because of tumor recurrence or treatment-related complications. Two patients had uncontrolled and enlarged melanomas; their eyes were enucleated 6 months after GKS. Two other patients suffered from severe retinal detachment and retinal hemorrhage; in one case the eye was enucleated 10 months post-GKS and in the other case 29 months after radiosurgery. In the fifth patient, the eye globe was enucleated 48 months after GKS because neovascularized glaucoma developed. In the whole group of patients, the eye retention rate was 86.4% (19 of 22 patients) 2 years after GKS and 77.3% (17 of 22 patients) 5 years after GKS (Fig. 2). The eye retention rate was analyzed according to patient age and sex, tumor volume, and tumor margin dose, but this failed to prove any statistical relationship among variables ($p > 0.05$).

Local Tumor Control Rate and Changes in Tumor Volume

A significant reduction in tumor volume was observed after GKS, but the volume increased in 2 patients. Thus, the overall local tumor control rate, defined as stable or reduced tumor thickness, was 90.9%. The mean tumor thickness before GKS was 9.53 mm (range 5.1–15.0 mm), and the cumulative 1-year and 2-year mean tumor-thickness reduction rates were 18.8% and 42.8%, respectively. We measured changes in tumor volume using the formula for the calculation of ellipsoid volume. The cumulative 1-year mean volume reduction rate was 41.8% (range 4.1%–100%) in the 20 patients in whom there was local tumor control. In the final follow-up, the mean volume reduction rate was 63.7% (Fig. 3). The melanomas disappeared almost completely in 5 patients, and the mean complete remission period was 5.2 months after GKS. A case in which tumor regression recurred 13 months after GKS is illustrated in Fig. 4. Unfortunately, 2 patients'

Fig. 2. Kaplan-Meier cumulative curves for overall eye retention in 22 patients.

eyeballs were enucleated because of uncontrolled uveal melanomas.

Overall Survival

The overall 5-year survival rate was 90.9% (20 of 22 patients) in our study. One patient died of causes related to liver metastasis from the uveal melanoma 4 months after GKS, and another patient died of lung cancer unrelated to the melanoma 22 months after radiosurgery. We analyzed patient survival according to age, sex, tumor volume, and margin dose; however, no relationship was found among these variables ($p > 0.05$) (Table 2).

Visual Acuity

A significant reduction in visual acuity was observed. Before GKS, visual acuity, determined using the Snellen chart, ranged from light perception to 1.2 (median 0.6). After treatment, visual acuity ranged from blindness to 0.9. Even though overall visual acuity was reduced after GKS in 21 of 22 patients, 14 patients (63.6%) exhibited preserved visual function better than hand-movement perception, which could be considered an advantage of radiosurgery. Only 1 patient who had recognized light before GKS became blind after the procedure. One patient displayed a slight improvement in vision, from 0.6 to 0.9 during 6 years after radiosurgery.

Other Side Effects After Gamma Knife Surgery

Radiation-related side effects were evaluated ophthalmologically and on imaging studies at regular intervals by ophthalmologists and neurosurgeons. Subsequent ocular complications occurred in 18 of 22 patients. The most frequent side effect was cataract in 9 (40.9%) of 22 patients, which was easily managed by ophthalmologists.

Fig. 3. Tumor volume changes during the follow-up in 20 patients. (Two cases whose volume had increased were excluded.)

Other complications included radiation-related retinopathy (5 cases), retinal detachment (2 cases), glaucoma (2 cases), and vitreous hemorrhage (2 cases). Some patients suffered from 2 or more concurrent complications. We could not find any significant relationship among any of

the side effects and several factors studied, such as radiation dose, tumor location, and tumor volume ($p > 0.05$).

Discussion

The selection of treatment for uveal melanomas is made in accordance with the general health status of the patient along with local findings related to the tumor, such as its stage and character; nevertheless, the disease is still considered difficult to treat.¹⁰ Various treatment modalities for uveal melanoma have been described in the literature. In recent years, eye globe-sparing techniques have become more widespread, and these include photocoagulation, transpupillary thermotherapy, radiotherapy, local resection, chemotherapy, immunotherapy, and stereotactic radiosurgery.^{2,5,6,12,22,23}

Besides the advantages of being less invasive and better tolerated by the patient, GKS can preserve the globe and restore visual function. In addition, it is a single-day treatment that can be completed within a few hours. On the other hand, GKS could deliver a dose to adjacent radiosensitive intraocular organs that is higher than they can tolerate, and it could potentially increase the chance of distant metastasis by not eliminating the melanoma itself. Previous retrospective series, in which the outcomes of GKS in the treatment of uveal melanoma were evaluated, have shown mixed results.^{4,7,15,16,19,21,24,28,29}

Modorati et al.¹⁸ reported that the 3-year probability of survival for uveal melanoma after GKS was 88.8% and the 5-year probability of survival was 81.9%. Fakiris et al.⁹ showed that the 3- and 5-year overall survival rates were 86% and 55%, respectively. These 3- and 5-year cumulative survival rates are comparable to those reported by others in cases of melanomas treated with GKS.^{15,19,23,28,29}

Fig. 4. **A:** Coronal contrast-enhanced T1-weighted MR image revealing a uveal melanoma situated at the inferior wall of the orbit before GKS (single arrow). **B:** Contrast-enhanced MR image obtained 13 months after GKS, showing nearly complete regression of the tumor. **C:** Fundoscopic views revealing an elevated yellowish subretinal mass (double arrows). **D:** Thirteen months after GKS a residual flat scar can be observed in the same area as the previous mass (double arrows).

TABLE 2: Survival according to variables*

Factor	Category	No. of Cases	1-Yr Survival	2-Yr Survival
age (yrs)	≤50	11	11	10
	>50	11	10	10
sex	male	12	11	10
	female	10	10	10
tumor location	anterior to equator	8	7	6
	posterior to equator	8	8	8
	both sides of equator	6	6	6
dose at tumor margin (Gy)	≤45	10	10	10
	>45	12	11	10
tumor vol (mm ³)	≤500	9	8	7
	>500	13	13	13
laterality	rt	13	12	12
	lt	9	9	8
total		22	21	20

* $p > 0.05$ for all factors.

In our study, the overall 5-year survival rate was 90.9% (20 of 22 patients). One patient died 4 months after GKS of causes related to liver metastasis from the uveal melanoma; the cause of death in the other patient, who died 22 months after GKS, was lung cancer unrelated to the melanoma. If we only consider the patient whose death was associated with melanoma, the survival rate is raised to 95.5% (21 of 22 patients). Cumulative 5-year survival after primary enucleation was reported to range from 31.45% to 65.2%,^{7,11} and Dinca et al.⁷ reported that no survival difference was observed between GKS and primary enucleation therapy. Also, no statistically significant differences were found in survival between patients treated by cobalt plaque therapy and those treated by enucleation.¹ Margo et al.¹⁷ concluded that there was no difference in 5-year survival rates in patients with medium-sized choroidal melanoma who were treated by iodine-125 brachytherapy or enucleation. There is still debate on the most effective modality for treating uveal melanomas. We believe that GKS would be a good method, given the good cosmetic result and quality of life that it provides the patient.

In a series of 81 patients in whom GKS was used in the treatment of uveal melanomas, Simonová et al.²⁴ achieved an 84% local tumor control rate at 10 months after GKS by applying a minimum dose of 31.4 Gy. Similarly, Modorati and colleagues¹⁸ achieved 91% tumor control in a group of 78 patients treated by GKS with 30–50 Gy of radiation at the tumor periphery. However, high complication rates were observed, including enucleation (10.3%), retinal detachment (33.3%), and glaucoma (18.7%). In our study, local tumor control was achieved in 20 (90.9%) of 22 patients, and the cumulative rates of tumor thickness regression were 18.8% in the 1st year and 42.8% in the 2nd year after GKS. Simonová et al.²⁴ reported that patient age, tumor location, dissemination of disease, and applied minimum dose were identified as having a significant influence on patient survival. In our study, we could not find any significant values among age,

sex, tumor margin dose, and tumor volume affecting survival.

A wide range of radiation doses was used in published series of GKS for uveal melanomas. Higher doses were used in earlier series, but there has been a general trend toward dose deescalation. Langmann et al.¹⁵ showed that a reduction in the dose directed to the tumor periphery from 50 to 40 Gy had no effect on the local tumor control rate, and this could minimize subsequent side effects. Mueller et al.¹⁹ reported that current treatments were performed using 25 Gy at 50% isodose to the tumor margin. We used a tumor margin dose that ranged from 20.0 to 67.5 Gy, and a mean dose 45.6 Gy, which includes the higher doses we used at the beginning of this study period.

The eye is a very radiosensitive organ, and it is not surprising that GKS can cause radiation-induced complications. The radiation tolerance of the optic nerve has been well defined in other radiosurgical procedures. The tolerance dose of the optic nerve is in the range of 8 to 10 Gy.^{13,20} However, the limits of an acceptable radiation dose are not clear for other tissues such as the retina, sclera, and iris. Even though radiation-induced complications involving the lens could be easily treated, atrophy of the optic nerve, corneal ulcers, and secondary glaucoma could represent far more serious problems.²⁴ In our series, ocular complications occurred in 18 of 22 patients. While the tumor control rate was similar to those of other series, the incidence of complications seems to be somewhat higher. These results may be related to the relatively higher tumor marginal dose. However, as shown in Table 3, no significant difference was noted in the tumor control rate when the radiation dose was changed. It seems that it is more reasonable to prescribe a lower radiation dose than the mean radiation dose used in our study to reduce any possible complications.

The rate of enucleation has been reported to range from 6% at the 2-year follow-up to 19% at 8 years af-

TABLE 3: Literature review of uveal melanomas treated by GKS*

Authors & Year	No. of Patients	Dose (Gy)	FU (mos)	Control Rate (%)	Complication Rate (%)	Initial Tumor Vol (mm ³)	Eye Retention Rate (%)
Mueller et al., 2000	35	25	12–20	97.0	NA	800	94.3
Langmann et al., 2000	60	45–80	16–94	93.0	55.0	NA	85.0
Simonová et al., 2002	75	20–76.5	10–74	87.0	NA	640	81.0
Fakiris et al., 2007	19	40	7.3–81	94.4	69.0	240	94.4
Modorati et al., 2009	78	30–50	17.6–60.6	91.0	80.8	NA	89.7
Toktas et al., 2010	35	30	13–57	94.3	56.9	397	91.4
current study	22	20–67.5	3–126	90.9	81.8	877	77.3

* FU = follow-up; NA = not available.

ter various treatment methods.^{2,3,8,27} In our study, the rate of enucleation was 22.7% (5 of 22 patients) at 5-year follow-up after GKS. In 2 patients, the eye globes were enucleated due to tumor recurrence and in 3 others due to subsequent GKS-related complications (severe retinal detachment in 2 patients and neovascularized glaucoma in 1 patient). The eye retention rate was 77.3% (17 of 22 patients), which is similar to results reported by others.^{15,18,24}

Conclusions

Gamma Knife surgery provided excellent local control of uveal melanomas with remarkable decreases in volume. In our study, a local tumor control rate of 90.9% and a globe preservation rate of 77.3% were achieved. The overall minor and major complication rate was 81.8% (18 of 22 patients), and we observed a higher rate of complications with a higher radiation dose.

Gamma Knife surgery is a safe and minimally invasive method that uses an optimal radiation dose for the treatment of uveal melanomas. This procedure not only preserves the eyeball and its potential visual function, but also decreases the potential for hematological dissemination and achieves sufficient local tumor control with a gradual reduction in volume.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Chang, Park. Acquisition of data: Kang. Analysis and interpretation of data: Chang, Kang, Lee. Drafting the article: Kang. Critically revising the article: Chang. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Chang. Statistical analysis: Kang. Administrative/technical/material support: Kang.

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