# Long-Term Outcomes of Gamma Knife Radiosurgery for Cystic Vestibular Schwannomas

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OBJECTIVE: **Vestibular schwannomas (VSs) can either be solid or contain variable amounts of cystic components. It has been established that gamma knife radiosurgery (GKRS) is an effective treatment modality for solid VSs. However, in the case of cystic VS, given the somewhat unpredictable growth of the cystic portion of these tumors, microsurgery has often been preferred to GKRS in the management of cystic VS. However, to date, a relative paucity of data evaluating the outcomes after GKRS for cystic VS has been available. In the present study, we reviewed our experience treating cystic VSs with GKRS and evaluated the results.**

METHODS: **The data from patients with a diagnosis of cystic VS who had undergone GKRS from 1999 to 2018 were analyzed. Only those patients who had undergone GKRS as the initial treatment of cystic VSs were included in the present study. Patients who had undergone previous surgical treatment were excluded. The cystic VSs were divided into intratumoral and peritumoral cysts.**

RESULTS: **A total of 24 patients were enrolled in the present study. The mean age was 60.8 ± 2.4 years (range, 38–82 years). The mean follow-up period was 55.8 ± 8.1 months (range, 8–145 months). Of the 24 patients, 11 were men. The control rate after GKRS for cystic VSs was 75%. The 5-year progression-free rate was 70%. Six patients had presented with an increasing lesion size after GKS. Of these 6 patients, 2 underwent surgical treatment and 1 underwent repeat GKRS. No statistically significant differences were found between the control rate and cystic type ($P = 0.093$).**

CONCLUSION: **The results from the present study have demonstrated that GKRS is an effective treatment modality for cystic VSs.**

## INTRODUCTION

Vestibular schwannoma (VS) is a benign brain tumor with a total prevalence of 0.02%–0.07%.[1-4] VSs can be either solid or contain variable amounts of cystic components.[5,6] Many studies have shown that gamma knife radiosurgery (GKRS) is an effective treatment of solid VS.[7-14] However, with cystic VS, complications can arise owing to an unexpected increase in cyst size after radiation surgery.[15,16] Therefore, surgical treatment has been preferred to GKRS for cystic VSs.

Previous studies have reported an increased cyst size after radiation surgery[16-19]; however, the results of those studies have been controversial owing to the paucity of data. In addition, only a few studies have considered the cyst location (intratumoral or peritumoral) in the analysis. However, this classification is important in selecting the target for GKRS.

In the present study, we analyzed the long-term outcomes of patients who had undergone GKRS as a primary treatment of cystic VS. We also sought to identify the prognostic factors and compared the outcomes between intratumoral and peritumoral cystic VS.

## METHODS

From January 1999 to December 2018, 389 patients had undergone GKRS for VS at our Gamma Knife Center. Of these, 24 patients with cystic VS had undergone GKRS as the primary treatment modality. Patients who had undergone surgery before GKRS were excluded from the present study. Thus, 24 patients (11 men and 13 women) were selected for the present study. The mean age was 60.8 ± 11.9 years (range, 38–82 years), and the mean follow-up period was 55.8 ± 8.1 months (range, 8–145 months; Table 1).

The patients underwent magnetic resonance imaging (MRI) using a Leksell stereotactic instrument (Elekta Instrument, Stockholm, Sweden). We used the Leksell KULA system (Elekta Instrument AB) until January 2002; thereafter, we used the Leksell GammaPlan system, version 10.1 (Elekta Instrument AB). All the patients who had undergone GKRS for VS underwent follow-up

**Key words**
- Cysts
- Gamma knife radiosurgery
- Postoperative complications
- Vestibular schwannoma

**Abbreviations and Acronyms**
GKRS: Gamma knife radiosurgery
MRI: Magnetic resonance imaging
VS: Vestibular schwannoma

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**Table 1.** Demographic and Clinical Characteristics of 24 Patients with Cystic Vestibular Schwannoma

| Characteristic | Value |
|---|---|
| Age (years) | |
| Mean ± SD | 60.8 ± 11.9 |
| Range | 38–82 |
| Sex (*n*) | |
| Male | 11 |
| Female | 13 |
| Follow-up period (months) | |
| Mean ± SD | 55.8 ± 8.1 |
| Range | 8–145 |
| Target volume ($cm^3$) | |
| Mean ± SD | 3.5 ± 3.0 |
| Range | 0.7–16 |
| Prescription dose (Gy) | |
| Mean ± SD | 13.2 ± 1.2 |
| Range | 10–15 |
| Radiological finding | |
| Intratumoral cyst | 17 |
| Peritumoral cyst | 7 |

SD, standard deviation.

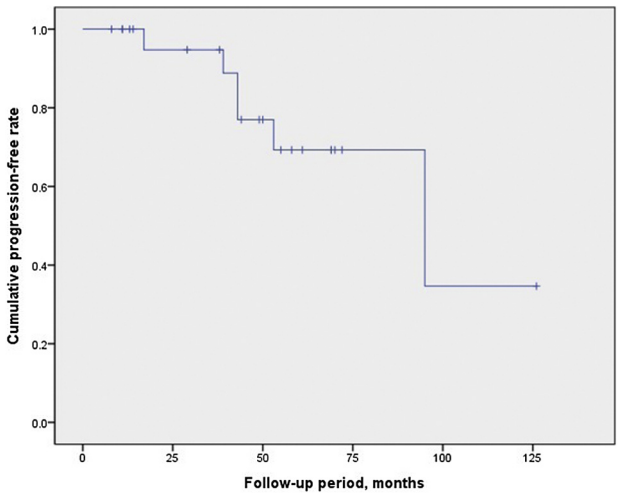


**Figure 1.** Kaplan-Meier graph presenting the cumulative progression-free rate of patients with cystic vestibular schwannomas who had undergone gamma knife radiosurgery.

MRI for treatment evaluation at 6 months postoperatively and annually thereafter.

Treatment failure was defined as an increase in lesion size after GKRS at the last follow-up MRI compared with the initial volume. An increase in size within 1 year after GKRS was excluded because of the possibility of pseudoprogression.

To assess the risk factors associated with failure, the following factors were analyzed: patient demographics (e.g., age, sex), GKRS profile (e.g., prescription dose, target volume), and cyst location (i.e., intratumoral vs. peritumoral). We defined cystic VS as VS containing dominant intratumoral or peritumoral cysts occupying >30% of the total tumor volume. The tumor and cyst volumes were estimated using the GammaPlan system (Elekta Instrument AB). We also defined intratumoral cysts as those cysts completely inside the tumor mass, and peritumoral cysts as those cysts with the cyst wall protruding outward from the margin of the tumor mass.

These factors were assessed using the $\chi^2$ test, Student *t* test, and Kaplan-Meier survival analysis. A final multivariate analysis was performed using logistic regression analysis. SPSS, version 21.0 (IBM Corp., Armonk, New York, USA) was used for all calculations, with a *P* value $< 0.05$ considered statistically significant.

## RESULTS

The tumor control rate of GKRS for all 389 cases of VS in our center was 84%. Of the 24 patients with cystic VS, tumor control was observed in 18 (75%). Six patients experienced tumor progression. Of those 6 patients, 2 underwent surgery and 1 underwent repeat GKRS. The 5-year progression-free rate was 70% (Figure 1).

For GKRS, the prescription dose volume included the entire enhancing tumor mass. Intratumoral cysts were also included in the target. For tumors with peritumoral cysts, only the tumor mass was included as the target, except for the cystic portion. The mean target volume was 3.5 ± 3.7 $cm^3$ (range, 0.7–16 $cm^3$), and the mean prescription dose was 13.2 ± 1.2 Gy (range, 10–15 Gy). One patient with a large size cystic VS had undergone GKRS without surgery because of the high risk of surgical treatment owing to a heart problem. Because the size was large and adjacent to the brain stem, it was treated with a low dose of 10 Gy to prevent the development of complications.

The radiological features showed that 17 patients had intratumoral cysts and 7 had peritumoral cysts. Univariate analysis revealed no statistically significant prognostic factors. Tumor control was observed in 14 patients with intratumoral cysts and 3 patients with peritumoral cysts; however, the difference was not statistically significant ($P = 0.307$; Table 2, Figure 2).

Of the 24 patients, 7 showed tumor regrowth on follow-up MRI. The onset of regrowth was 20.4 ± 12.2 months (range, 7–37) after GKRS. Of the 7 tumors, 4 were controlled, 2 underwent surgical treatment, and 1 was controlled after repeated GKRS.

Multivariate analysis revealed the prescription dose was the only significant prognostic factor. The dose was slightly greater in the group of patients with tumor progression (odds ratio, 31.5; Table 3). However, the Kaplan-Meier analysis according to the prescription dose did not show any statistical significance (Figure 3).

**Table 2.** Univariate Analysis of Prognostic Factors for Patients with Controlled or Progressing Tumors

| Variable | Controlled Tumor ($n$ = 18) | Progressing Tumor ($n$ = 6) | $P$ Value |
|---|---|---|---|
| Age (years) | 60.6 ± 12.4 | 61.8 ± 11.6 | 0.823 |
| Sex ($n$) | | | 0.59 |
| Male | 8 | 3 | |
| Female | 10 | 3 | |
| Target volume ($cm^3$) | 3.7 ± 4.2 | 3.1 ± 2.5 | 0.64 |
| Prescription dose (Gy) | 13.0 ± 1.2 | 13.8 ± 1.3 | 0.206 |
| Cyst location ($n$) | | | 0.307 |
| Intratumoral | 14 | 3 | |
| Peritumoral | 4 | 3 | |

Data presented as mean ± standard deviation, unless otherwise noted.

**Table 3.** Multivariate Analysis of Prognostic Factors

| Factor | $P$ Value | OR | 95% CI |
|---|---|---|---|
| Age | 0.471 | 0.945 | 0.810—1.102 |
| Sex (male vs. female) | 0.507 | 0.356 | 0.017—7.505 |
| Target volume | 0.121 | 1.0 | 1.000—1.001 |
| Prescription dose | 0.045* | 31.5 | 1.085—918.990 |
| Cyst location (intratumoral vs. peritumoral) | 0.052 | 406.1 | 0.944—174773.134 |

OR, odds ratio; CI, confidence interval.
*$P < 0.05$.

### Representative Case

A 64-year-old woman had presented with dizziness. A brain MRI scan revealed a VS (size, 25 × 35 × 21 mm) at the right cerebellopontine angle, with intracanalicular extension. Multiple cystic lesions were present inside and outside the tumor. The cyst wall was compressing the pons and cerebellum. GKRS was performed, with the tumor lesion as the target, excluding the peritumoral cysts. The 50% marginal dose was 12.5 Gy (Figure 4). The follow-up MRI scan showed tumor size reduction, peritumoral cyst control, and relief of the pons and cerebellum compression at 42 months after GKRS (Figure 5).

## DISCUSSION

VS with a cystic component is not uncommon. However, until recently, no universally accepted definition of cystic VS existed. Controversy has existed regarding the safety and effectiveness of GKRS for cystic VS versus solid VS because of the sudden increase in size of the cystic portion after GKRS. The sudden increase in size can result in neurological symptoms and the possibility of additional surgical removal. In 1996, Pendl et al.[20] defined cystic VS as a tumor with a cystic component greater than two thirds of the total tumor volume. In their study, 6 patients with cystic VS who had undergone GKRS with follow-up for ≥18 months showed significant enlargement of the cystic portion (by 50%) compared with the 4-month data and progressive neurological decline requiring surgical treatment.[20]

Nevertheless, a number of studies have been reported by many investigators on various aspects of the management and outcomes of GKRS for cystic VS versus solid VS. Shirato et al.[21] summarized the tumor expansion rate and long-term tumor control after

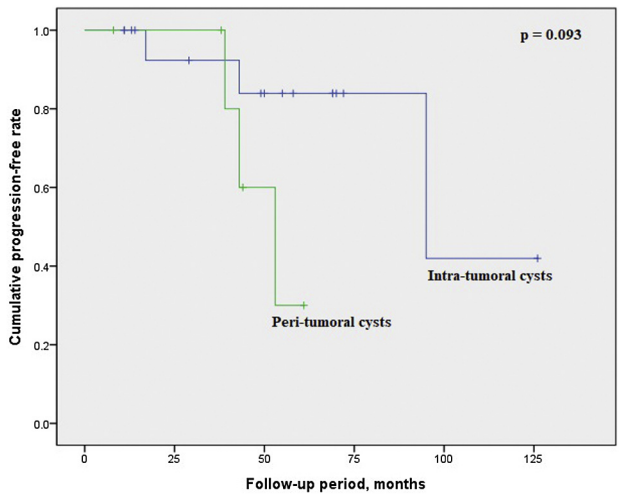


**Figure 2.** Kaplan-Meier graph presenting the cumulative progression-free rate of patients with intratumoral cysts versus patients with peritumoral cysts.

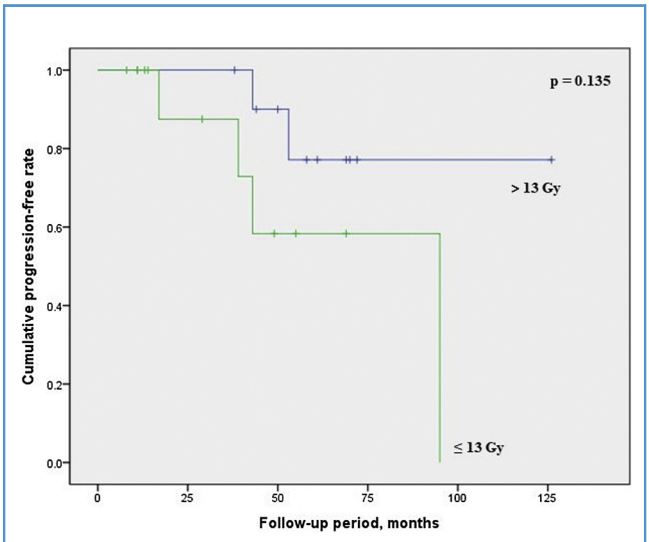


**Figure 3.** Kaplan-Meier graph presenting the cumulative progression-free rate according to the prescription dose.

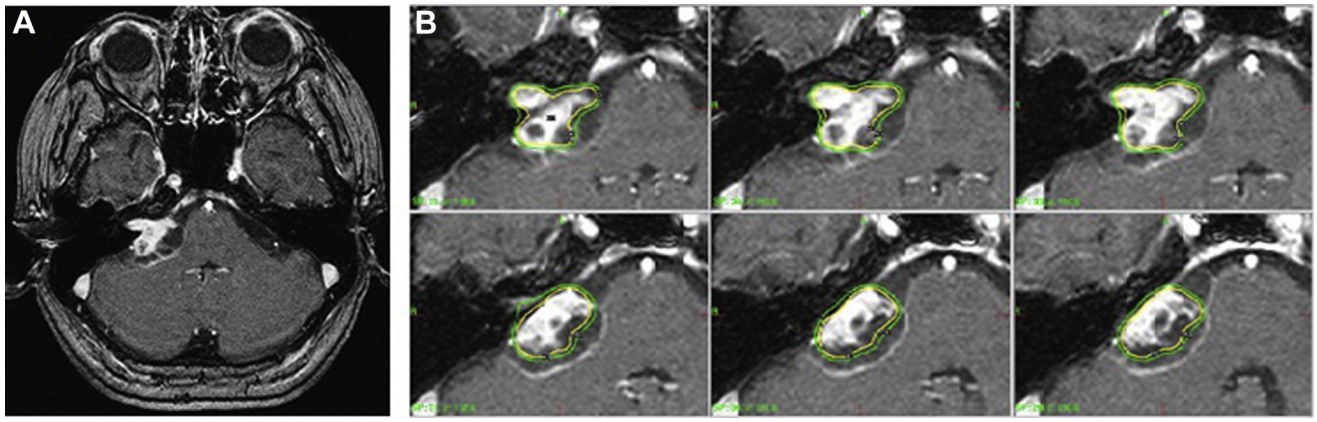


**Figure 4.** A case of right cystic vestibular schwannoma. (**A**) Magnetic resonance imaging findings at gamma knife radiosurgery. (**B**) Dosimetry plan for the tumor, excluding the peritumoral cysts. The *green line* represents the 50% marginal dose.

fractionated stereotactic radiotherapy in both solid and cystic VS groups. Transient tumor enlargement within 2 years after treatment occurred more frequently in the cystic VS group than in the solid VS group.[21] However, the subsequent tumor reduction rate was better in the cystic VS group when the follow-up period was >3 years.[21] Frisch et al.[18] matched 20 cases of cystic tumors treated with GKRS with 20 cases of solid VS (control group). They reported that the 5-year overall control rate was similar at 90%.[18] The results of these studies suggest that no statistically significant difference exists in the ultimate tumor control rate between solid and cystic VSs after GKRS. Therefore, GKRS can be considered as a treatment option.

In the study by Hasegawa et al.,[22] the 10-year progression-free survival rate was >92% for the solid and cystic VS groups both. In addition, multivariate analysis showed that a cystic tumor was not a risk factor for stereotactic radiosurgery failure. However, they had defined cystic tumors as "mixed tumors with cystic components,"[22] unlike other studies, which had defined the specific criteria for cystic VS, which we reviewed previously.

Bowden et al.[23] studied 219 patients with VS that had been classified as homogeneous, microcystic, and macrocystic types during a 10-year period. More than 5 years of tumor control was found in 95% of all types, regardless of the radiological features.[23] Although the presence of cystic changes was a negative predictor of the tumor response to stereotactic radiosurgery, macrocystic VSs showed the greatest volumetric reduction.[23] These data support the long-term follow-up results that GKRS is a safe and effective treatment of all VSs (solid and cystic) and that it would be worth trying GKRS for cystic VSs even if cystic involvement is a negative prognostic factor for GKRS. Our data showed a 75% tumor control rate, relatively lower than that of previous studies. However, we only analyzed the data from patients who had not undergone surgical treatment to allow treatment of patients with large tumor sizes. Furthermore, because most tumors and peritumoral cysts were adjacent to the brain stem in our study, we could not use the optimal radiation dose for that lesion. Therefore, the effect of GKRS might have been lower than expected.

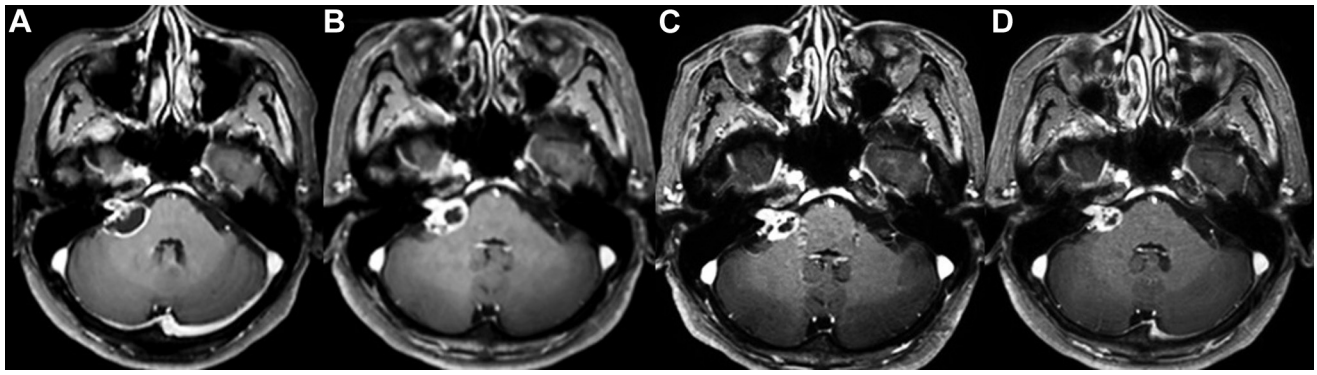


**Figure 5.** Follow-up magnetic resonance imaging findings at (**A**) 6 months, (**B**) 18 months, (**C**) 30 months, and (**D**) 42 months after gamma knife radiosurgery.

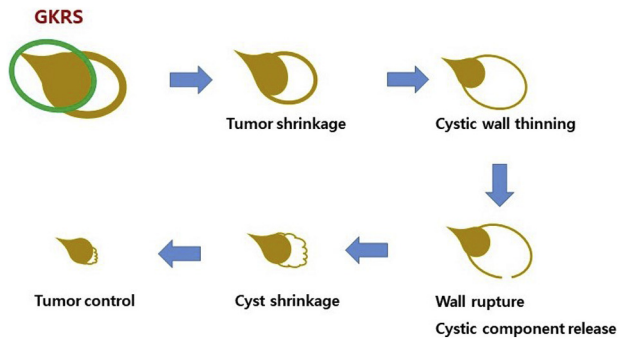


**Figure 6.** Schematics of the mechanism of peritumoral cyst shrinkage after gamma knife radiosurgery (GKRS). The *green line* represents the prescription dose.

The mechanism of cyst enlargement after GKRS is still unclear. Thompson et al.[24] suggested that cyst enlargement might occur owing to the transudation of vessels in the tumor wall. Coagulation necrosis of tumor tissue could also increase the osmotic tendency. Shuto and Matsunaga[19] reported that reddish lesions around the tumor were found during surgery for 2 cases of VS with cystic enlargement after GKRS. In addition, dilated capillary vessels with wall degeneration were observed on microscopic examination.[19] They suggested that cyst formation and enlargement might not be a part of the natural course of VS but, rather, a late complication of GKRS for extra-axial benign tumors such as VS.[19]

We found tumor control in 4 of 7 patients with VS with peritumoral cysts. When targeting the tumor for GKRS, we excluded the cysts from the target. However, both tumor and peritumoral cyst shrinkage was observed on the follow-up radiological examinations. The reason the nonirradiated cystic area was reduced is unclear. The possible mechanisms are as follows. First, tumor shrinkage occurs after tumor targeting and irradiation. Because the cyst wall on the side of brain stem was adherent to the surrounding structures, the cyst wall will be pulled and will become gradually thinner as the tumor shrinks. As a result of the cyst wall thinning, wall rupture will eventually result in release of the internal cystic component, causing cyst shrinkage. Therefore, the entire tumor, including the cysts, can be controlled (**Figure 6**). This hypothesis was based on the follow-up MRI scans only; thus, no clear evidence is available. However, in several cases, we found that the peritumoral cysts, which were excluded from the GKRS target, had decreased or been eliminated without any manipulation. Thus, we consider that the cyst wall tore owing to the reduction in the tumor size.

The present study had a few limitations. First, no consensus definition of a cystic tumor has been established. Although we defined cystic VS as VS containing dominant intratumoral or peritumoral cysts occupying >30% of the total tumor diameter using the greatest linear axial cerebellopontine angle dimension, the effect of a smaller cyst should not be overlooked. Second, the present study lacked the large numbers necessary for robust statistical comparison. Nonetheless, our research is important because, unlike previous studies, we analyzed tumor cyst patterns separately. In particular, peritumoral cysts, which have previously been an indication for surgical treatment, shrank after GKRS in our study. Therefore, a sufficient therapeutic effect can be expected.

## CONCLUSION

Although a risk of cyst enlargement accompanied by neurological symptoms exists, which might require surgical intervention, GKRS was safe and effective as a treatment modality for cystic VS in the present study. When targeting only tumors other than peritumoral cysts, we observed that the tumor and cyst could both shrink together in long-term follow-up examinations. Therefore, GKRS can be considered as a primary treatment option more positively for patients with VS with peritumoral cysts, with the support of careful follow-up.

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