Tumor shrinkage of vestibular schwannomas after Gamma Knife surgery: results after more than 5 years of follow-up

Clinical article

Osamu Nagano, M.D., Toru Serizawa, M.D., Yoshinori Higuchi, M.D., Shinji Matsuda, M.D., Makoto Sato, R.T., Iwao Yamakami, M.D., Koichi Okiyama, M.D., Junichi Ono, M.D., and Naokatsu Saeki, M.D.

1Gamma Knife House and 3Department of Neurosurgery, Chiba Cardiovascular Center, Ichihara; 2Tokyo Gamma Unit Center Tsukiji Neurological Clinic, Tokyo; 3Department of Neurological Surgery, Chiba University Graduate School of Medicine, Chiba; and 4Department of Neurosurgery, Chiba Central Medical Center, Chiba, Japan

Object. The authors prospectively analyzed volume changes in vestibular schwannomas (VSs) after Gamma Knife surgery (GKS).

Methods. Among 104 VSs treated by GKS at the Chiba Cardiovascular Center between 1998 and 2004, 87 consecutively treated unilateral VSs observed on follow-up MR imaging for at least 5 years were analyzed. These lesions were harbored by 31 men and 56 women, with a mean age of 58.6 years (range 29–80 years). The Gd-enhanced volume of each lesion was measured serially every 3 months during the 1st year and every 6 months thereafter using GammaPlan or SurgiPlan. The frequency and degree of volume shrinkage were documented and possible prognostic factors were analyzed.

Results. The mean tumor volume at GKS was 2.5 cm$^3$ (range 0.1–13.2 cm$^3$). The lesions were irradiated by directing a mean dose of 12.0 Gy (range 10.5–13.0 Gy) to the tumor margin, which was located at the mean 52.2% isodose line (range 50%–67% isodose line). The mean follow-up period was 7.5 years (range 5.0–11.1 years). Peak tumor volume expansion was most frequently observed at 8.6 months after GKS and averaged 58% (range 0%–613%). Five years after GKS, the mean reduction in tumor volume was 31%, and 9 tumors still remained larger than their initial volumes. Tumors that homogeneously enhanced on MR images displayed less shrinkage than other tumors.

Conclusions. Most VSs exhibit shrinkage 5 years after GKS. The mean volume reduction in this series was 31%. These results indicate that careful serial follow-up is necessary for patients who harbor tumors that display homogeneous enhancement on MR images and patients whose tumors continue to expand in size after GKS.

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Key Words • vestibular schwannoma • Gamma Knife surgery • radiosurgery • tumor volume • tumor shrinkage

Recently, GKS for small VSs became accepted as an efficacious treatment that produces high tumor control rates with extremely low incidences of severe complications. However, occasionally we observe an initial enlargement of these lesion accompanied by central low intensity on neuroimaging studies within 1 year after treatment; this is known as "temporary enlargement," "tumor expansion," "transient swelling," or "transient expansion." Thereafter, tumor volume gradually decreases over a 1-year period. In this study, we focused on tumor volume changes, prospectively analyzing degrees of volume reduction in VSs after GKS.

Abbreviations used in this paper: GKS = Gamma Knife surgery; VS = vestibular schwannoma.

Methods

Patient Population

Among 104 patients with unilateral VSs treated by GKS at the Chiba Cardiovascular Center between 1998 and 2004, 87 patients (84%) participated in follow-up with MR imaging for at least 5 years; these cases are the focus of this analysis. Seventeen other patients were excluded from this study because we only obtained long-term follow-up images and were unable to evaluate tumor volume changes, especially during the 1st year after GKS. Patient characteristics are shown in Table 1. There were 31 men and 56 women, with a mean age of 58.6 years (median 59 years, range 29–80 years). Twenty-seven patients (31%) had undergone resection before GKS.
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TABLE 1: Characteristics of patients with VSs who underwent GKS

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>total no. of patients</td>
<td>87</td>
</tr>
<tr>
<td>age (yrs) range</td>
<td>20–80</td>
</tr>
<tr>
<td>mean (median)</td>
<td>58.6 (59)</td>
</tr>
<tr>
<td>sex</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>31</td>
</tr>
<tr>
<td>female</td>
<td>56</td>
</tr>
<tr>
<td>no. of patients w/ previous surgery</td>
<td>27</td>
</tr>
</tbody>
</table>

After each patient received local anesthesia with adequate sedation, GKS started with placement of the patient’s head in a rigid-fixation Leksell G stereotactic frame (Elekta AB). Treatment planning was performed using the Leksell GammaPlan by 1 neurosurgeon (T.S.) in all cases. For dose planning, we always use contrast-enhanced T1-weighted gradient-echo axial MR sequences (TR 45 msec, TE 3.5 msec, flip angle 30°, field of view 260 mm, slice thickness 2 mm, interslice gap 0 mm, and matrix 400 × 382) and continuous interference steady-state sequences and CT scanning. Seventy-five patients were treated using the Gamma Knife model B and 12 using the model C (Elekta AB). We used the multiple isocenter technique and set the optimal peripheral dose at 12 Gy directed to the 50% isodose line, changing this value according to individual situations such as tumor size.

Follow-up neuroimaging included contrast-enhanced T1-weighted gradient-echo MR imaging sequences, which were the same as those used for dose planning. For each lesion, the Gd-enhanced volume was measured serially every 3 months during the 1st year and every 6 months thereafter, using noninvasive volumetric software (GammaPlan or SugiPlan, Elekta AB). The volume measurements were made by 2 neurosurgeons (T.S. and O.N.). Error was estimated to be < 5%, as verified by phantom measurements. A probability value of < 0.05 was defined as statistically significant. Neurological deterioration involving trigeminal and facial nerve functions was examined along with follow-up neuroimages by 1 neurosurgeon (T.S.). Trigeminal neuropathy was defined as any facial dysesthesia within the ipsilateral trigeminal nerve distribution. Facial neuropathy was defined as any deterioration in House-Brackmann facial nerve grade.

Results

Radiosurgical Techniques

The radiosurgical parameters are shown in Table 2. The mean tumor volume at GKS was 2.5 cm³ (median 1.9 cm³, range 0.1–13.2 cm³). The mean peripheral dose was 12 Gy (median 12 Gy, range 10.5–13 Gy). The isodose line for the tumor margin varied from 50% to 67% (mean 52.2%, median 50%). The peripheral dose coincided with 12 Gy directed to the 50% isodose line in 76 cases. Iso-center numbers ranged from 4 to 39 (mean 16, median 15 isocenters), and the mean Paddick conformity index was 0.8 (median 0.81, range 0.43–0.93). Twenty-nine tumors (33%) displayed homogeneous enhancement. The mean follow-up period was 7.5 years (median 7.1 years, range 5.0–11.1 years).

Changes in Tumor Volume

In this study, 67 tumors (77%) exhibited transient expansion (≥ 10% increase followed later by tumor shrinkage). The maximum tumor expansion rates are shown in Fig. 2. The volume increase was < 10% (no significant increase) in 20 tumors, 10%–30% in 19, 31%–50% in 19, 51%–100% in 15, and > 100% in 14 tumors (mean 58%, range 0%–613%). Changes in volume ratios are shown in Fig. 3. Peak tumor expansion was most frequently observed at 8.6 months after GKS. One-half of the 87 tumors regressed to their initial size within 1.5 years. The mean volume reduction was 31% at 5 years after GKS. Nine tumors (10.3%) remained larger than they had been before GKS as long as 5 years after treatment.

Tumor volume changes stratified by patient age and sex, previous surgery, tumor volume, conformity index, and MR imaging findings are presented in Fig. 4. A homogeneously enhancing tumor seems to be the greatest risk factor for lack of tumor shrinkage. There was a statistically significant difference between homogeneously and heterogeneously enhanced VSs.

We divided volume changes into 3 categories. 1) Transient expansion followed by progressive tumor shrinkage occurred in 60 patients. Maximal transient expansion was generally seen at 6–12 months, although in 16 patients prolonged tumor expansion was documented for up to 24 months before shrinkage began. 2) Direct tumor shrinkage (no transient expansion) was seen in 20 patients. 3) Repeated increases in tumor volume (that is transient expansions) occurred > 2 years after GKS in 7 patients. One patient in this latter group underwent microsurgery 6 years after GKS because of intractable trigeminal neuralgia. Histological examination showed typical schwannoma with partial myxoid degeneration. Changes in volume ratios are shown in Fig. 5.

Functional Outcomes

Facial dysesthesia was triggered by a tumor pushing
against the trigeminal nerve. All MR images obtained in the 17 patients with trigeminal neuropathy showed tumor tissue abutting the trigeminal nerve before or after treatment, and in 7 patients, this tissue subsequently separated from the trigeminal nerve as the tumor shrank. Improvement in trigeminal neuropathy was seen a few months after the tumor had moved away from the trigeminal nerve. Fourteen patients experienced facial paresis as tumor volume increased. The most common problem of this type

**TABLE 2: Radiosurgical parameters***

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>tumor volume (cm³)</td>
<td>range 0.1–13.2</td>
</tr>
<tr>
<td>mean (median)</td>
<td>2.5 (1.9)</td>
</tr>
<tr>
<td>peripheral dose (Gy)</td>
<td>range 10.5–13.0</td>
</tr>
<tr>
<td>mean (median)</td>
<td>12.0 (12.0)</td>
</tr>
<tr>
<td>Paddick conformity index</td>
<td>range 0.43–0.93</td>
</tr>
<tr>
<td>mean (median)</td>
<td>0.80 (0.81)</td>
</tr>
<tr>
<td>MRI findings (no. of tumors)</td>
<td>homogeneous enhancement 29</td>
</tr>
<tr>
<td>heterogeneous enhancement</td>
<td>58</td>
</tr>
<tr>
<td>follow-up (yrs)</td>
<td>range 5.0–11.1</td>
</tr>
<tr>
<td>mean (median)</td>
<td>7.5 (7.1)</td>
</tr>
</tbody>
</table>

* MRI = MR imaging.

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**Fig. 1.** Serial contrast-enhanced axial T1-weighted MR images obtained before GKS. Homogeneous enhancement (upper) was defined as the lack of a low-intensity area in the tumor. Heterogeneous enhancement (lower) was defined as the presence of a low-intensity area in the tumor.

**Fig. 2.** Pie chart showing the frequencies of various degrees of maximal transient tumor expansion.
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...was facial spasm (10 patients [71%]). In this study, all patients with facial palsy experienced a rapid and full recovery to their pre-GKS status as the tumor shrank.

**Discussion**

We found that transient tumor expansion, with peak expansion usually observed at 6–12 months, represented a mean increase of nearly 50% in volume compared with initial (pre-GKS) tumor volume. Incidences of transient tumor expansion reportedly occur in between 39% and 62% of patients based on 3D measurements obtained using the GammaPlan. In this study, significant transient tumor expansion ($\geq 10\%$ increase) was documented in 77% of patients. This difference in percentages of patients with transient tumor expansion is attributable to differing observation periods and cutoff values.

**Fig. 3.** Graph depicting changes in tumor volume ratios in 87 patients. Mean tumor volume had increased by 28% at 6 months but decreased to the initial volume by 1.5 years after GKS. At 5 years postoperatively, the mean tumor volume was reduced by 31% compared with the tumor's original size.

**Fig. 4.** Graphs showing tumor volume changes over a 5-year period according to various factors: patient age (A), patient sex (B), previous surgery (C), tumor volume (D), conformity index (E), and MR imaging findings (F). Homogeneous enhancement seems to be the greatest risk factor for a lack of tumor shrinkage. The difference between homogeneously and heterogeneously enhanced tumors is statistically significant.
After a period of expansion, most tumors shrink. We found a volume reduction of 31% at 5 years after GKS. Yu et al. reported a 46.8% shrinkage rate in 92% of their VS cases 30 months after GKS, and Wowra et al. reported a 35% shrinkage rate after 4 years. These findings are similar to our own. We believe that taking 3D measurements should be the standard method of documenting volume changes in VS, because 2D measurements are not suitable for detecting small changes in volume. For example, a 10% increase in diameter is equivalent to a 33% volume expansion.

In our series, 7 tumors in 7 patients repeatedly enlarged after the initial transient expansion. In 5 of the 7 tumors, only the cystic components of the lesions enlarged, whereas the solid components diminished in size. In the other 2 tumors, expansion of an intratumoral low-intensity area was observed on MR images. Although we did not seek to clarify the mechanism of repeated tumor expansion in this study, several authors have suggested increased tumor size after GKS is caused by radiation-induced tumor necrosis, chronic intratumoral bleeding resulting from delayed radiation injury, minor hemorrhage from a cystic component, and/or a biological response to radiation.

Our analyses seem to indicate that homogeneous tumor enhancement on MR images is associated with a risk of insufficient tumor shrinkage. Homogeneous enhancement was identified as an independent factor in the multivariate analysis (p = 0.0022). Moon et al. wrote about 2 types of tissue found in these tumors.

In VS, 2 tissue types can be distinguished. One, Antoni Type A, has a compact texture with interwoven bundles of long bipolar spindle cells that have a tendency to palisade. The other, Antoni Type B, is characterized by its loose texture and is composed of uniform, small, somewhat satellite cells. It is known that the cystic portion of VS is located in the Antoni Type B area, which is softer than the Type A area.

Yang et al. reported that the tumor control rate of cystic VSs is higher than that of solid VSs after GKS. We suggest that there are biological differences between VSs that display homogeneous enhancement and those that exhibit heterogeneous enhancement. Additional follow-up of patients harboring VSs is anticipated to provide more insights into the risk factors associated with volume changes after GKS.

Conclusions
Most VSs display shrinkage at 5 years after GKS. In this series, the mean volume reduction was 31%. Our findings indicate that careful serial follow-up is essential for cases in which the tumor displays homogeneous enhancement on MR images and for cases in which the tumor repeatedly expands in size after GKS.

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: Osamu, Serizawa, Higuchi. Reviewed final version of the manuscript and approved it for submission: all authors. Administrative/technical/material support: Sato. Study supervision: Sacki.

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Address correspondence to: Osamu Nagano, M.D., Gamma Knife House, Chiba Cardiovascular Center, 575, Tsurumai, Ichihara, Chiba Prefecture 290-0512, Japan. email: osamu5@x9.so-net.ne.jp.