Transient expansion of vestibular schwannoma following stereotactic radiosurgery

Clinical article

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Object. The authors prospectively analyzed volume changes in vestibular schwannomas (VSs) after stereotactic radiosurgery.

Methods. One hundred consecutive patients with unilateral VS treated with Gamma Knife surgery (GKS) at Chiba Cardiovascular Center between 1998 and 2006 were analyzed in this study. For each lesion the Gd-enhanced volume was measured serially every 3 months in the 1st year, then every 6 months thereafter, using volumetric software. The frequency and degree of transient tumor expansion were documented and possible prognostic factors were analyzed. Concurrently, neurological deterioration involving trigeminal, facial, and cochlear nerve functions were also assessed.

Results. The mean observation period was 65 months (range 25–100 months). There were 32 men and 68 women, whose mean age was 59.1 years (range 29–80 years). Tumor volumes at GKS averaged 2.7 cm³ (range 0.1–13.2 cm³), and the lesions were irradiated at the mean 52.2% isodose line for the tumor margin (range 50–67%), with a mean dose of 12.2 Gy (range 10.5–13 Gy) at the periphery. The tumor volume was increased by 23% at 3 months and 27% at 6 months. Tumors shrank to their initial size over a mean period of 12 months. The maximum volume increase was < 10% (no significant increase) in 26 patients, 10–30% in 23, 30–50% in 22, 50–100% in 16, and > 100% in 13. The peak tumor expansion averaged 47% (range 0–613%). A high-dose (≥ 3.5 Gy/min) treatment appears to be the greatest risk factor for transient tumor expansion, although the difference did not reach statistical significance. Transient facial palsy and facial dysesthesia correlated strongly with tumor expansion, but only half of the hearing loss was coincident with this phenomenon.

Conclusions. Transient expansion of VSs after GKS was found to be much more frequent than previously reported, strongly suggesting a correlation with deterioration of facial and trigeminal nerve functions.

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Key words: • facial nerve function • Gamma Knife surgery • stereotactic radiosurgery • transient tumor expansion • trigeminal nerve dysesthesia • vestibular schwannoma

Recently, SRS for small VSs has been established as being efficacious, with high tumor control rates and extremely low incidences of severe complications. However, we occasionally encounter transient cranial neuropathies, such as facial dysesthesia, facial spasm, tinnitus, vertigo, and hearing loss. Typical MR images show initial enlargement with central low intensity within 1 year after treatment, termed “temporary enlargement,”14 “tumor expansion,”7,6 or “transient expansion.”14 Thereafter, the tumor volume gradually decreases over a 1-year period. In this study, we prospectively analyzed the frequency and degree of transient expansion, and the relationships between tumor expansion and cranial neuropathies are discussed.

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

Methods

Patient Population

One hundred consecutive patients with unilateral VS treated with GKS at Chiba Cardiovascular Center between 1998 and 2006 were analyzed in this study. Patient characteristics are shown in Table 1, and radiosurgical parameters in Table 2. There were 32 men and 68 women, with a mean age of 59.1 years (median 59 years, range 29–80 years). Thirty-five patients (35%) had undergone resection.

The SRS was performed using the standard GKS technique.11,12 The procedure begins with the patient’s head being placed in a rigid fixation Leksell G stereotactic frame (Elekta Instruments) after induction of local anesthesia with adequate sedation. Treatment planning was performed using the Leksell Gamma Plan by one
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), as well as continuous-interference steady-state sequences and CT scanning. All patients were treated using the Gamma Knife model B (Elekta Instruments). The multiple-isocenter technique was used and the standard prescription dose was 50% 12 Gy in the periphery.

Follow-up neuroimaging included contrast-enhanced T1-weighted gradient-echo MR sequences, 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 6 months thereafter, using non-invasive volumetric software (GammaPlan or SurgiPlan). The multiple-isocenter technique was used and the standard prescription dose was 50% 12 Gy in the periphery.

Results

Radiosurgical Techniques

The tumor volume at GKS averaged 2.7 cm$^3$ (median 2, range 0.1–13.2 cm$^3$). The mean peripheral dose was 12.2 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%). Isocenter numbers were 4–42 (mean 16.7, median 17) and the mean Paddick conformity index was 0.80 (range 0.43–0.93). The mean observation period was 65 months (median 66, range 25–100 months).

Maximum tumor expansion rates are shown in Fig. 1. The volume increase was < 10% (no significant increase) in 26 cases, 10–30% in 23, 30–50% in 22, 50–100% in 16, and > 100% in 13. Peak expansion was most frequently observed at 6.4 months after GKS and averaged 47% (range 0–613%) of the initial volume (Fig. 2). Figure 3 demonstrates tumor shrinkage to the initial size. Half the tumors regressed to their initial size within 1 year. Nine percent of tumors were still larger than they had been initially as long as 5 years after treatment. These patients experienced transient expansion, but the tumor remained

TABLE 1

<table>
<thead>
<tr>
<th>Variable</th>
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<tbody>
<tr>
<td>age in yrs range</td>
<td>29–80</td>
</tr>
<tr>
<td>mean (median)</td>
<td>59.1 (59)</td>
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<tr>
<td>sex (no.) male</td>
<td>32</td>
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<tr>
<td>female</td>
<td>68</td>
</tr>
<tr>
<td>tumor laterality (no.)</td>
<td>46</td>
</tr>
<tr>
<td>lt</td>
<td>46</td>
</tr>
<tr>
<td>rt</td>
<td>54</td>
</tr>
<tr>
<td>no. w/ previous op</td>
<td>35</td>
</tr>
<tr>
<td>follow-up period in mos range</td>
<td>25–100</td>
</tr>
<tr>
<td>mean (median)</td>
<td>65 (66)</td>
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TABLE 2

<table>
<thead>
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<th>Variable</th>
<th>Value</th>
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<tr>
<td>tumor vol in cm$^3$ range</td>
<td>0.1–13.2</td>
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<tr>
<td>mean (median)</td>
<td>2.7 (2.0)</td>
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<tr>
<td>peripheral dose in Gy range</td>
<td>10.5–13.0</td>
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<tr>
<td>mean (median)</td>
<td>12.2 (12.0)</td>
</tr>
<tr>
<td>Paddick conformity index range</td>
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<tr>
<td>mean (median)</td>
<td>0.80 (0.86)</td>
</tr>
<tr>
<td>dose rate in Gy/min range</td>
<td>1.66–3.67</td>
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<tr>
<td>mean (median)</td>
<td>2.67 (2.73)</td>
</tr>
</tbody>
</table>

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. Acoustic neuropathy was defined as any decline in Gardner–Robertson hearing class for patients with at least Class IV hearing.

The frequency and degree of tumor expansion were documented. The interval between peak expansion and shrinkage to the initial size was analyzed using the Kaplan–Meier method. To analyze prognostic factors, we assessed the following dichotomized variables: age (< 60 vs ≥ 60 years), sex (male vs female), tumor laterality (right vs left), previous surgery (yes vs no), tumor volume (< 2 vs ≥ 2 cm$^3$), peripheral dose (< 12 vs ≥ 12 Gy), Paddick conformity index (< 0.8 vs ≥ 0.8), and dose rate (< 3.5 vs ≥ 3.5 Gy/min). Factors affecting tumor expansion were evaluated using a logistic regression model. We compared the onsets of these neurological deteriorations between patients with 30% versus ≥ 30% increment in tumor volume by using the log-rank test. A probability value of < 0.05 was defined as statistically significant.
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Tumor volume changes according to age, sex, laterality, previous surgery, tumor volume, peripheral dose, conformity index, and dose rate are presented in Fig. 4. A high dose rate appears to be the greatest risk factor for tumor expansion, but logistic regression did not reveal a statistically significant difference ($p = 0.877$).

There were statistically significant differences in the incidences of trigeminal, facial, and cochlear nerve dysfunctions between patients with tumor expansion < 30% versus $\geq 30\%$ (Fig. 5). Facial dysesthesia was triggered by the tumor attaching to the trigeminal nerve. All MR images of 17 patients with trigeminal neuropathy showed tumor tissue attached to the trigeminal nerve before or after treatment, and in 7 patients this tissue subsequently detached from the trigeminal nerve as the tumor shrank. Improvement of trigeminal neuropathy required a few months after the tumor had been detached from the trigeminal nerve. Twenty patients experienced facial paresis as tumor volume increased. The most common problem of this type was facial spasm (17 patients; 85%). In this study, all patients with facial palsy showed rapid and full recovery to their pre-GKS status, as the tumor shrank. Hearing was preserved in 60% of 28 patients with useful hearing. Half of hearing loss corresponded to tumor expansion, but hearing seldom normalized as the tumor shrank (only 1 patient experienced recovery). The incidence of radiation-induced edema of the cerebellum was 14% in our study. This occurred ~ 6 months after irradiation, corresponding to transient expansion, and decreased as the tumor shrank.

**Illustrative Case**

This 64-year-old woman had an expanding residual VS after 2 operations. The tumor (3.8 cm$^3$) was treated with a peripheral dose of 50% 12 Gy (Fig. 6A). The lesion then gradually increased in size (Fig. 6B and C). Nine months after treatment, she experienced facial spasm (House–Brackmann Grade III) and dysesthesia. Admission MR imaging demonstrated that the tumor had doubled in size and showed central low intensity (Fig. 6D). Fifteen months after GKS, expansion was maximal. The tumor was nearly 4 times its original size (Fig. 6E). Thereafter, the tumor shrank to its initial size (Fig. 6F), and continues to shrink (Fig. 6G). The patient recovered from the facial paresis as the tumor regressed over a 2-year period, and facial dysesthesia had nearly disappeared 3 years after GKS.

**Discussion**

Incidences of transient tumor expansion reportedly range from 17 to 62%. In contrast, in this study we found that 74% of patients with VS after GKS show significant transient tumor expansion (≥ 10% increase). This difference is attributable to differing observation periods, measurement methods, and cutoff values. We evaluated tumor volumes using MR imaging every 3 months after GKS with 3D measurements based on GammaPlan or SurgiPlan. In most previous reports, tumor volumes were measured by 2D methods with follow-up imaging at 6 months. This difference indicates that 2D measurement is not suitable for detecting small changes in volume. For example, a 10% increase in diameter is equivalent to a 33% volume expansion.

We found the incidence of transient expansion, with peak expansion usually being observed at 6–9 months, to represent a volume increase to nearly 50% of the initial volume. Irradiation did induce biological changes in the tumors. We did not clarify the mechanism of transient tumor expansion in this study. Several authors have suggested that increased tumor size after GKS could be caused by radiation-induced tumor necrosis, chronic intratumoral bleeding resulting from delayed radiation injury, and/or a biological response to radiation.

**Cranial Nerve Dysfunctions**

Recently, there have been several reports on transient expansion after SRS for VS, but little is known about neurological deterioration associated with this phenomenon. In the early 1990s, facial nerve paresis after SRS was
considered to result directly from radiation injury, and the treatment dose was thus reduced from 15 Gy to the present 12–13 Gy.3,17,22 The use of MR imaging for dose planning, combined with CT scanning and improved dose-planning software, has greatly reduced direct radiation injury.13,15,17 Despite these advances, transient facial spasm does occasionally manifest within 1 year after SRS. In our institute, under close observation, we found that 20% of patients

Fig. 4. Graphs showing tumor volume changes according to various factors: age, sex, laterality, previous surgery, tumor volume, peripheral dose, conformity index, and dose rate. A high dose rate seems to be the greatest risk factor for transient expansion. However, logistic regression failed to detect any statistically significant difference. HR = hazard ratio.
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experienced facial spasm and that it was associated with transient tumor expansion (Fig. 5B). Facial spasm usually started with the lower eyelid, and then extended to the angle of the mouth. This spasm is a temporary phenomenon related to facial paresis, which has been described as facial myokymia.9,10 The facial spasm disappears as the tumor shrinks.

Trigeminal nerve dysfunction was also strongly related to transient tumor expansion (Fig. 5A). The trigeminal nerve disturbance usually manifested as ipsilateral facial dysesthesia without motor paresis. Patients described the sensation as like anesthesia for a dental procedure or as a pins-and-needles sensation, and typical trigeminal neuralgia was occasionally recognized. This symptom improved as the tumor shrank. However, trigeminal dysesthesia usually improved later than facial paresis, often taking several months or even years to resolve. It is important to inform patients thoroughly about these potential sequelae. Furthermore, we explain to our patients the temporal relationship between transient expansion and these symptoms.

On the other hand, half of hearing loss is attributable to post-GKS deterioration, which is not related to tumor expansion (Fig. 5C). This observation suggests that acoustic nerves may be injured with even lower doses than for the fifth and seventh cranial nerves.2 However, only 1 of our patients experienced hearing loss after GKS; this patient’s hearing normalized as the tumor shrank. To

Fig. 5. Kaplan–Meier curves demonstrating the cranial neuropathy-free survival rate based on facial dysesthesia, facial nerve dysfunction, and hearing preservation, comparing patients with a < 30% increase to those with a ≥ 30% increase in tumor volume. The differences are statistically significant.

Fig. 6. Serial contrast-enhanced axial T1-weighted MR images obtained in a 64-year-old woman with a right VS who underwent GKS. A: Dose-planning image for a right-sided VS. Line (inset) indicates the 50% isodose curve. The initial tumor volume was 3.8 cm³. B: On an MR image obtained 3 months later, there was an 81% expansion (6.9 cm³) with central low intensity. C: Image obtained 6 months post-GKS, demonstrating a 97% expansion (7.5 cm³). D: Image obtained 9 months post-GKS, showing a 105% expansion (7.8 cm³). E: Image obtained 15 months post-GKS, demonstrating maximum expansion (276%, 14.3 cm³). F: Image obtained 4 years post-GKS, showing shrinkage to nearly the initial size (3.7 cm³). G: Image obtained 6 years post-GKS, showing remarkable tumor regression (3.1 cm³).
preserve hearing, we focused on avoiding high-dose irradiation to the acoustic and/or cochlear nerve during dose planning.

Our analyses suggested that high-dose treatments (≥3.5 Gy/min) apparently carry the greatest risk of transient tumor expansion (p = 0.877), but the difference was not statistically significant. Additional follow-up of patients with VS will allow us to draw a more definitive conclusion regarding risk factors associated with transient tumor expansion after GKS.

Conclusions

Transient expansion after GKS for VS was found to be much more frequent than previously reported, strongly suggesting a correlation with deterioration of facial and trigeminal nerve functions. However, the present study revealed neither prognostic factors influencing this phenomenon nor the underlying mechanisms.

Disclaimer

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

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References


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