Outpatient gamma knife surgery for vestibular schwannoma: definition of the therapeutic profile based on a 10-year experience

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Object. The purpose of the study was to define the therapeutic profile of outpatient gamma knife surgery (GKS) for vestibular schwannoma (VS) by using sequential tumor volumetry to quantify changes following treatment.

Methods. A total of 111 patients met the inclusion criteria. The median follow-up duration was 7 years (range 5–9.6 years). Thirty-seven patients (33%) had undergone surgery before GKS and 10 (9%) had neurofibromatosis Type 2 (NF2). The median VS volume was 1.6 cm³ (range 0.08–8.7 cm³).

The actuarial 6-year tumor control rate after a single GKS treatment was 95%. Tumor swelling was observed in 43 patients (38.7%). Recurrence was significantly associated with NF2 (p < 0.003) and the reduced dose (p < 0.03) delivered to these tumors. The incidence of facial nerve neuropathy was mainly determined by surgery prior to GKS (p < 0.0001). Facial nerve radiation toxicity was mild and transient. No permanent facial nerve toxicity was observed. Trigeminal neuropathy occurred in 13 patients, and this was correlated with the VS volume (p < 0.02). The median hearing loss was −10 dB (range +20 dB to −70 dB). The risk of hearing loss was correlated with age and transient tumor swelling (p < 0.05) but not with dose parameters or NF2.

Conclusions. Outpatient GKS is feasible, effective, and safe. Its therapeutic profile compares favorably with that of microsurgery.

KEY WORDS • gamma knife surgery • vestibular schwannoma • tumor volumetry

In 1971 Lars Leksell reported the first radiosurgical treatment of a patient with an "acoustic neuroma." During the subsequent three decades, GKS for VS (a more correct term for the tumor commonly termed acoustic neuroma) has evolved. Today, it has become a widely conducted treatment alternative to microsurgery; however, there is still room for improvement in the way the results of microsurgery and radiosurgery are presented. With the current widespread availability of MR imaging, the detection rate of VS has risen, which means the socioeconomic impact of therapy for VS is also affected. A major difference between surgery and radiosurgery is that the tumor’s mass is removed at operation whereas radiosurgery merely stops tumor growth, at least in the first instance, which leaves dead and dying neoplastic tissue in situ to be disposed of by the body’s own regenerative mechanisms. Typically GKS causes either tumor stabilization or shrinkage, although absence of tumor growth and even spontaneous regression of the untreated VS have also been observed. Therefore, one could speculate that GKS may facilitate or even induce natural mechanisms of tumor control and indeed there is evidence that apoptosis, at least in part, is involved in the GKS-induced response of VS.

In this context, careful monitoring of tumor volume seems not only reasonable but even mandatory. Today, measurement of VS volume is possible because of digital imaging methods such as MR imaging and computerized tomography scanning. By using STV, the growth of VS has been confirmed after a comparatively short follow-up period, despite evidence that they are slow-growing lesions. After GKS, VS shrinkage with or without a period of transient tumor swelling has been detected using STV. Despite the capacity to assess the response of VS to GKS objectively, however, STV has not become a universally accepted measure of outcome in patients in whom VS is treated with GKS. The purpose of this study was to describe the therapeutic outcome of outpatient GKS for VS including long-term follow-up information with STV.

Clinical Material and Methods

By May 1999 a consecutive series of 174 patients with VS had been treated with outpatient GKS. The treatments were performed using the Leksell gamma knife model B.
Vestibular schwannoma: outpatient GKS

and the planning was undertaken using Leksell GammaPlan (versions 2.01–5.12). A 1.0-tesla Siemens Expert MR imager was used for treatment planning and for follow-up examinations in all patients. For these studies we used the three-dimensional mp3 sequence as described elsewhere. Computerized tomography served as supplementary imaging but was of no consequence to this study.

The GammaPlan software was used for all tumor volumetry. All the measurements were performed by one investigator (B.W.). To assess the variability of the volumetry, a reference tumor was selected and measured repeatedly (10 times) for a period of more than 5 years after GKS with six sequential follow-up intervals.

The dose planning strategy included multiple isocenters with the steepest dose gradient at the anterior margin of the VS (Fig. 1). Treatment failure was defined as the need for a further therapy if the VS increased significantly in size and if tumor swelling was excluded. For the definition of tumor swelling (mostly transient), a cutoff value of +10% volume increase after GKS was accepted in this study.

Inclusion criteria were the presence of a VS with documented growth or clearly progressive symptoms. The tumor volume was less than 10 cm. All patients attended serial follow-up examinations at the same center where they were treated at regular intervals (3–6, 18–24, and 30–36 months after GKS and then every 2 years). One hundred eleven (63.8%) of the consecutive 174 patients met these criteria and form the basis of the study. All clinical, treatment-related, and all follow-up data (including STV measurements) were stored prospectively in a computerized database. The minimum follow-up period was 5 years. For statistical analysis the StatView program (SAS Institute, Cary, NC) was used.

Results

The results of the volumetry of the reference case are summarized in Table 1. The percentage standard deviation was 9.3% (range 4.9–13.6%) for all measurements. In the reference case a VS shrinkage of 88% was calculated 6 years after GKS (Fig. 2). Transient tumor swelling was observed between 3 and 9 months after GKS. At this time interval, the tumor volume increased transiently up to 180% of the treated target volume (Fig. 2).

Follow-up information was available for 111 patients (100%) (Table 2). The median follow-up interval was 7 years (range 5–9.6 years). Thirty-seven patients (33%) had undergone surgery before GKS whereas 74 (66.7%) were treated by GKS alone. Ten patients (9%) had NF2. The median VS volume was 1.6 cm (range 0.08–8.7 cm); the margin tumor dose was 13 Gy (10–16 Gy) placed in a median peripheral isodose of 55% (range 45–85%). The medi-

<table>
<thead>
<tr>
<th>Date (mos after GKS)</th>
<th>Median</th>
<th>Mean</th>
<th>Mean (% of T0)</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
<th>% SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 (T0)†</td>
<td>1.30</td>
<td>1.28</td>
<td>100</td>
<td>0.06</td>
<td>1.20</td>
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<tr>
<td>3.4</td>
<td>1.62</td>
<td>1.58</td>
<td>123</td>
<td>0.08</td>
<td>1.50</td>
<td>1.70</td>
<td>5.0</td>
</tr>
<tr>
<td>9.4</td>
<td>2.30†</td>
<td>2.30†</td>
<td>180†</td>
<td>0.16</td>
<td>2.00</td>
<td>2.50</td>
<td>7.1</td>
</tr>
<tr>
<td>21.4</td>
<td>1.10</td>
<td>1.14</td>
<td>89</td>
<td>0.07</td>
<td>1.10</td>
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<td>34.2</td>
<td>0.42</td>
<td>0.42</td>
<td>33</td>
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<td>0.36</td>
<td>0.46</td>
<td>7.4</td>
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<td>47.3</td>
<td>0.29</td>
<td>0.27</td>
<td>21</td>
<td>0.05</td>
<td>0.19</td>
<td>0.33</td>
<td>17.1</td>
</tr>
<tr>
<td>69.3</td>
<td>0.16</td>
<td>0.16</td>
<td>12</td>
<td>0.02</td>
<td>0.12</td>
<td>0.19</td>
<td>13.6</td>
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* SD = standard deviation.  † T0 = Date of GKS. ‡ Indicates VS swelling.
an number of isocenters per patient was eight (range one–25). The median conformity index according to Paddick was 0.68 (range 0.26–1) (Table 2).

The median VS shrinkage was 65.5% 4 years after GKS (Table 3). The actuarial 6-year tumor control rate for all patients who had undergone a single GKS treatment was 95%. Ten of 11 recurrent VS were retreated by additional GKS, and one patient underwent microsurgery. Taking into account the retreatments, all tumors were controlled. Recurrence of VS after GKS was associated with NF2 (p = 0.003) and a lower dose (p = 0.03) delivered to these tumors (Fig. 3 and Table 4). Tumor swelling was observed in 43 patients (38.7%).

The incidence of facial nerve neuropathy was mainly determined by surgery prior to GKS in that 75% of operated patients were so affected (p < 0.0001) (Table 4). Facial nerve radiation toxicity due to GKS was mild and transient and was observed in three patients with additional risk factors (previous surgery, NF2, and cerebrovascular disease). There was no permanent facial nerve neuropathy after GKS. Trigeminal neuropathy occurred in 13 patients. It was correlated with tumor volume (p < 0.02). The median hearing loss was −10 dB (range +20 dB to −70 dB) as outlined in Table 3. The risk of hearing loss was correlated with age and transient tumor swelling (p < 0.05) but not with dose parameters or NF2.

**Discussion**

The benign natural course of VSs is their prominent feature. In general VSs are not life-threatening tumors. Initially, they cause functional symptoms and compromise the quality of life due to cranial nerve compression or irritation. After longer periods, they may also cause hydrocephalus and brainstem compression. Typically VSs do not grow continuously. There are often longer periods of very slow growth or growth arrest.1,4,8,12,17,20,25,31,33,34,48,49,51,55,57 Even spontaneous regression has been described in 6 to 13% of VS.4,17,51,55 Therefore, the appropriate time for any therapeutic intervention is a matter of debate.10

In radiosurgery the treated tumor tissue is left in situ. Different biological mechanisms may account for the modality’s final therapeutic result. The induction of apoptosis by GKS has been described,13,52 although there may be further reactions involved in the response of VS tissue to GKS. Imaging after GKS, for example, reveals more or less pro-

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**TABLE 2**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
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<tr>
<td>VS vol (cm³)</td>
<td>1.70</td>
<td>0.08</td>
<td>8.70</td>
</tr>
<tr>
<td>Dmax (Gy)</td>
<td>13.0</td>
<td>10.0</td>
<td>16.0</td>
</tr>
<tr>
<td>Dmin (Gy)</td>
<td>22.7</td>
<td>15.3</td>
<td>31.1</td>
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<tr>
<td>isodose (%)</td>
<td>55</td>
<td>45</td>
<td>85</td>
</tr>
<tr>
<td>PIV (cm³)</td>
<td>1.80</td>
<td>0.10</td>
<td>8.80</td>
</tr>
<tr>
<td>isocenters</td>
<td>8</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>C index</td>
<td>0.68</td>
<td>0.26</td>
<td>0.84</td>
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* C index = conformity index according to Paddick; Dmax = maximum tumor dose; Dmin = dose to the tumor margin; PIV = peripheral isodose volume.

† Isodose indicates the percentage of dose covering the tumor margin.

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**TABLE 3**

<table>
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<th>Parameter</th>
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<th>Min</th>
<th>Max</th>
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</thead>
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<tr>
<td>follow up (yrs)</td>
<td>7.0</td>
<td>5.1</td>
<td>9.5</td>
</tr>
<tr>
<td>last VS vol (cm³)</td>
<td>1.10</td>
<td>0.00</td>
<td>12.10</td>
</tr>
<tr>
<td>hearing loss (dB)</td>
<td>6.5</td>
<td>−25</td>
<td>76</td>
</tr>
</tbody>
</table>

**FIG. 3.** Actuarial Kaplan–Meier plot showing tumor control for sporadic and NF2 VSs after a single GKS treatment.
Vestibular schwannoma: outpatient GKS

TABLE 4
Incidence of facial paresis after microsurgery and after GKS: comparison of dose level (D_{min}) for sporadic VS and NF2 tumors

<table>
<thead>
<tr>
<th></th>
<th>Facial Paresis</th>
<th>p Value</th>
<th>D_{min} (Gy)</th>
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<tbody>
<tr>
<td>postsurgery</td>
<td>25 of 34</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>post-GKS</td>
<td>3 of 111</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>sporadic VS</td>
<td>101</td>
<td>&lt;0.04</td>
<td>13.0 ± 0.9</td>
</tr>
<tr>
<td>NF2</td>
<td>10</td>
<td>12.3 ± 1.0</td>
<td></td>
</tr>
</tbody>
</table>

nounced disruption of the interstitial perfusion. The effects of these biological mechanisms may be significant for the clinical and radiological results of GKS.

Traditionally radiosurgical success has been defined as the absence of further tumor growth—that is, tumor stabilization or shrinkage. The response of tumor tissue to GKS, however, is a dynamic process that may hinder the recognition of treatment failures. Several authors have reported increased tumor size after GKS. After the swelling period, most tumors reduced continuously to less than 2%. Our results also support the conclusion of Hudgins that "when patients other investigators. After the swelling period, most tumors increased tumor size after GKS; this swelling is transient in most patients, although it may last for up to 2 years. In the present study, the incidence of transient swelling was found in 39%. Swelling was defined as an increase in tumor volume of 10% or more with respect to the initial tumor volume. This is in line with the findings of other investigators. After the swelling period, most tumors shrink. After 4 years, we measured a volume reduction of 35%. Yu and colleagues reported a similar rate of shrinkage of 46.8% in 92% of their VS cases 30 months after GKS. Thus an overall control rate of 95% was found in our study. These findings are in agreement with other published results.

There has been a trend to lower treatment doses for VS during the past decade. In our study a reduced dose level was predominantly applied in patients with NF2 lesions involving the only hearing ear. In these patients an increased recurrence rate was recorded; thus, we urged physicians to be careful when using lower doses. Although radiosurgical retreatment is possible to increase the tumor control rate, according to our experience it is inevitably associated with complete hearing loss.

Sparing facial nerve function is another important issue in VS therapy. In the early days of GKS, the rate of facial nerve dysfunction was 30 to 40%. This rate has been reduced continuously to less than 2%. Our results also support the conclusion of Hudgins that "when patients prefer the preservation of facial nerve function, even if that requires leaving a tumor remnant, then GKS is a better treatment strategy than microsurgical resection." In the current series no patient suffered permanent facial nerve deficit after GKS.

The optimal therapy for hearing preservation remains a matter of debate. No prospective study including surgery, radiosurgery, and fractionated radiotherapy is available. Early GKS has been advocated. Superior results have been claimed for fractionated stereotactic radiotherapy despite some controversial observations and rather short follow-up periods. The results of microsurgery are difficult to interpret because of inhomogeneous reporting criteria and their dependence on the classification schemes used. On the other hand, progressive hearing loss is found also in nongrowing untreated VS. Thus, the available data in the literature permit the contention that GKS is not associated with an inferior hearing outcome compared with other treatment modalities.

Conclusions

Outpatient GKS is feasible, effective, and safe. Its therapeutic profile compares favorably with that of microsurgery and stereotactic radiation therapy. Tumor volumetry should be a routine part of follow up.


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