Long-term tumor control and cranial nerve outcomes following Gamma Knife surgery for larger-volume vestibular schwannomas

Clinical article

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Object. Gamma Knife surgery (GKS) for vestibular schwannoma (VS) is an accepted treatment for small- to medium-sized tumors, generally smaller than 2.5 cm in the maximum posterior fossa dimension. The purpose of this study was to evaluate the efficacy and toxicity of GKS for larger tumors.

Methods. Prospectively collected data were analyzed for 22 patients who had undergone GKS for VSs larger than 2.5 cm in the posterior fossa diameter between 1997 and 2006. No patient had symptomatic brainstem compression at the time of GKS. The median treated tumor volume was 9.4 cm³ (range 5.3–19.1 cm³). The median maximum posterior fossa diameter was 2.8 cm (range 2.5–3.8 cm). The median tumor margin dose was 12 Gy (range 12–14 Gy). Serial imaging, audiometry (10 patients with serviceable hearing pre-GKS), and clinical follow-up were available for a median of 66 months (range 26–121 months). Tumor control failure was defined as either a progressive increase in tumor diameter of at least 2 mm in any dimension or a later resection.

Results. Four patients met the criteria for GKS failure, including 1 patient who demonstrated sarcomatous degeneration more than 7 years after GKS and died 3 months after microsurgical debulking. An enlarging cystic component was the surgical indication in 1 of the 2 patients who required resection, although 27% of tumors (6 lesions) were cystic before GKS. The 3-year actuarial rate of tumor control, freedom from new facial neuropathy, and preservation of functional hearing were 86%, 92%, and 47%, respectively. At 5 years post-GKS, these rates decreased to 82%, 85%, and 28%, respectively. At the most recent follow-up, 91% of tumors were smaller than at the time of GKS and the median maximum posterior fossa diameter reduction was 26%. On multivariate analysis, none of the following factors was associated with GKS failure, new facial weakness, new trigeminal neuropathy, or loss of serviceable hearing: patient age, tumor volume, tumor margin dose, and preoperative cranial nerve dysfunction.

Conclusions. Single-session radiosurgery is a successful treatment for the majority of patients with larger VSs. Although tumor control rates are lower than those for smaller VSs managed with GKS, the cranial nerve morbidity of GKS is significantly lower than that typically achieved via resection of larger VSs.

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Key Words • vestibular schwannoma • acoustic neuroma • Gamma Knife • radiosurgery • stereotactic radiosurgery

Gamma Knife surgery is an accepted treatment option for patients with small- to medium-sized VSs.1,4,10,14,20,23,30 Typically, GKS yields low rates of facial and trigeminal neuropathy, good hearing preservation rates, and tumor control exceeding 95% for most sizes of VSs.4,8,9,14,20,23,29 Microsurgery is generally considered the best treatment for VSs larger than 2.5 cm in the posterior fossa dimension, for patients with symptomatic brainstem compression, and for those presenting with hydrocephalus.10,19,20,27,33 Several studies have documented increased morbidity following GKS for larger tumors, but the majority of these tumors were treated with higher tumor margin doses (16 Gy) than is generally used today.4,10,14,20,30 One study of VSs treated with contemporary radiosurgical doses (tumor margin doses of 12–13 Gy) reported only a 57% 5-year PFS for patients with tumors larger than 15 cm³ (24 tumors).14 A more recent GKS study of larger VSs (5–22 cm³, median volume 9 cm³) treated with a median margin dose of 12 Gy dem-
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onstrated an 87% tumor control rate at the last follow-up (median follow-up 36 months) with excellent preservation of facial nerve function (98%). In the present study, we report our results with GKS in treating larger VSs.

Methods

Patient Population

Between 1997 and 2006, 305 patients underwent GKS for VS at the Mayo Clinic in Rochester, Minnesota. Over this interval, we identified 22 patients with tumors larger than 2.5 cm in the maximum posterior fossa diameter, usually measured parallel to the petrous temporal bone (median treated volume > 9.4 cm³), and at least 24 months of follow-up. The study was conducted with the approval of the Mayo Clinic Institutional Review Board.

Data Collection

Patient demographics as well as pre- and post-GKS signs and symptoms, including the presence, character, and severity of cranial neuropathies (trigeminal, facial, cochlear, vestibular, and lower CNs) and cerebellar dysfunction, were collected from our prospectively maintained database. At all patient visits, facial nerve function was rated by the treating neurosurgeon using the HB grading scale. Hearing was graded according to the AAO-HNS classification. Gamma Knife surgery treatment parameters were recorded from the original treatment plan, including the number of isocenters, treatment volume, tumor margin dose, and prescription isodose level.

The maximum tumor size on the pre- and post-GKS MR imaging studies was measured in 3 linear dimensions: parallel to the petrous temporal bone at the level of the internal auditory canal, perpendicular to the petrous temporal bone at the level of the internal auditory canal, and the greatest superior-inferior dimension. We chose to use linear measurements because of sensitivity to tumor growth and because the inter-/intraobserver variability of linear measurements approaches that of 3D volumetric measurements for VSs that deform the brainstem or deviate the fourth ventricle. Magnetic resonance imaging examinations post-GKS are generally requested every 6 months for 1 year, annually for 4 years thereafter, and then every 2 years indefinitely. We requested audiograms at the time of follow-up MR imaging for patients who continued to have serviceable hearing (AAO-HNS Class A/B).

During the clinical and radiological follow-up period, we recorded the time-to-occurrence of specific postprocedural events including new persistent trigeminal neuropathy, temporary or permanent facial weakness of at least 1 HB grade, loss of serviceable hearing, new ataxia, vestibulopathy or imbalance, requirement for steroid therapy for radiation-induced edema, and radiographic or clinical GKS failure. We defined radiographic failure as an increase in the maximum tumor diameter by at least 2 mm on serial MR imaging examinations. Clinical failure was defined as the need for an additional VS-related intervention, such as resection or VP shunting.

Statistical Methods

Statistical analyses were performed using JMP software (version 9.0, 2010, SAS Institute, Inc.). The chi-square and Fisher exact tests were used to compare nominal variables before and after GKS. The paired Student t-test was used to compare tumor volumes before GKS with those at the 1-year and the last follow-up. A p < 0.05 was considered significant. Multivariate analysis was performed using nominal logistic regression to assess possible risk factors for GKS failure, new trigeminal neuropathy, and new facial weakness. The actuarial risk of GKS failure, loss of serviceable hearing, and new facial weakness were calculated using the Kaplan-Meier product-limit method.

Results

Patient Demographics and Treatment Parameters

The cohort was composed of 22 patients (13 men and 9 women). One patient had neurofibromatosis Type 2, and only 1 tumor in this patient met the study’s inclusion criteria. The mean age at GKS was 61.0 ± 15 years with an average 1.9-year lag between diagnosis and GKS. Presenting signs and symptoms are detailed in Table 1. Functional hearing (AAO-HNS Class A/B) and excellent facial nerve function (HB Grade I–II) were present before GKS in 10 (45%) and 21 (95%) patients, respectively. The median maximum extrameatal tumor dimension was 2.8 cm (range 2.5–3.8 cm), and more than one-quarter of the tumors had a prominent cystic component. One patient underwent VP shunting before GKS, and another had residual/recurrent tumor following a prior resection. The median treatment volume was 9.4 cm³ (range 5.3–19.1 cm³) utilizing a median of 13 isocenters (range 8–22 isocenters). The median tumor margin dose was 12 Gy (range 12–14 Gy). The median clinical and radiographic follow-up was 66 months (range 26–121 months). Two illustrative cases are featured in Fig. 1, each demonstrating a cystic change before GKS.

Tumor Control

Ten tumors (45%) were smaller at 1 year following GKS, and this number increased to 82% at the time of the last follow-up. The median maximum tumor dimension decreased significantly by the time of the last follow-up compared with both the baseline and 1-year follow-up

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>trigeminal neuropathy</td>
<td>13 (59)</td>
</tr>
<tr>
<td>HB grade</td>
<td></td>
</tr>
<tr>
<td>I–II</td>
<td>21 (95)</td>
</tr>
<tr>
<td>III–VI</td>
<td>1 (4)</td>
</tr>
<tr>
<td>ataxia/unsteadiness</td>
<td>5 (23)</td>
</tr>
<tr>
<td>AAO-HNS class</td>
<td></td>
</tr>
<tr>
<td>A/B</td>
<td>10 (45)</td>
</tr>
<tr>
<td>C/D</td>
<td>12 (54)</td>
</tr>
<tr>
<td>tinnitus</td>
<td>6 (27)</td>
</tr>
</tbody>
</table>
measurements (Table 2). The mode and timing of tumor control failure are detailed in Table 3. The 3- and 5-year actuarial rates of clinical and radiographic PFS were 86% and 82%, respectively (Fig. 2). The median GKS treatment volume in the 4 patients who met the criteria for GKS failure was 9.6 cm³ (range 8.2–19.1 cm³).

One death occurred during follow-up. This 59-year-old man had a rapidly enlarging tumor 7 years after GKS.37 He underwent microsurgical debulking, and pathological analysis identified the mass as a pleomorphic sarcoma. He awoke from surgery without a new neurological deficit but experienced a progressive neurological decline in the following weeks and died 3 months from the time of microsurgery. The patient also suffered an ankle fracture after a fall. She underwent excision of the cyst and subtotal tumor removal. Postoperatively, her gait and nausea improved. She retained the HB Grade II facial function she had had before GKS.

**Neurological Outcome**

Corticosteroid therapy for symptomatic radiation-induced changes in the brainstem and/or cerebellum was required in 3 patients (14%) for a median of 12 weeks (range 3–37 weeks).

Detailed CN morbidity and functional outcomes are shown in Table 3. Twenty patients (91%) had HB Grade I–II facial function at the time of the last follow-up. One patient had temporary facial nerve dysfunction, whereas 3 patients experienced a permanent decrement of at least 1 HB grade compared with before GKS. The median time to the worst post-GKS facial nerve function was 49 months (range 17–90 months). The 3- and 5-year actuarial rates of preserved baseline facial nerve function were 92% and 85%, respectively (Fig. 3).

Three (30%) of the 10 patients with serviceable hearing before GKS had retained AAO-HNS Class A or B hearing at the time of the last follow-up. Loss of serviceable hearing occurred at a median of 16 months (range 6–37 months) after GKS. The 3- and 5-year rates of maintenance of serviceable hearing were 47% and 28%, respectively (Fig. 4).

**Risk Factors for GKS Failure or Complication**

Multivariate analysis revealed no specific risk factors for GKS failure or post-GKS cranial neuropathy, including patient age, treatment volume, cystic tumor character, tumor margin dose, pre-GKS trigeminal or facial neuropathy, and pre-GKS hearing loss.

**Discussion**

There now exists substantial Level 2 and Level 3 evidence supporting GKS for the treatment of small- to medium-sized VSs.5,18,25,26,29,30,34,39 For larger tumors, a variety of treatment strategies exist including GKS, GTR, NTR (leaving a very small remnant of tumor capsule on the facial nerve or brainstem to hopefully maintain neurological function), STR with planned secondary GKS, STR with initial observation and repeat STR or GKS for regrowth, and so forth. In this series of larger VSs, we
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report an 82% 5-year PFS with 95% of patients achieving excellent facial nerve function and 30% of patients maintaining functional hearing. Before GKS alone can be considered a viable treatment strategy for select patients with larger VSs, these outcomes must be compared with those achieved using GKS for smaller VSs and using up-front surgical treatments for larger VSs.

Tumor Control

Long-term tumor control rates exceeding 93% after GKS for small- to medium-sized VSs are well established.9,14,23,29 In the first published study with contemporary margin radiation dosing (12–13 Gy), Flickinger and colleagues9 reported a 98.6% 6-year actuarial control rate for a cohort of 313 patients with a median tumor volume of 1.1 cm$^3$ followed up for a median of 24 months after GKS. However, only 36 patients (12%) in this series were followed up for at least 5 years. Hasegawa and colleagues14 confirmed excellent PFS, 93% at 5 years and 92% at 10 years, in their cohort with 317 patients followed up for a minimum of 5 years after GKS. These authors noted that most tumor control failures occurred within 36 months of GKS. Further, they identified 2 major risk factors for tumor control failure: a tumor volume exceeding 15 cm$^3$ (5-year PFS 57%) as well as brainstem compression and/or displacement of the fourth ventricle (5-year PFS 74%). Yang and colleagues40 recently reported an 87% tumor control rate at a median follow-up of 36 months for a cohort with 65 tumors measuring 3–4 cm in diameter, 26% of which were residual/recurrent VSs. In addition, 3 patients (5%) in that study required VP shunting for hydrocephalus that had developed after GKS. In the current study, we report a similar 5-year PFS of 82% for larger-volume VSs. The cumulative data available on the treatment of larger VSs using GKS show a higher failure rate compared with GKS treatment of smaller tumors. After radiosurgical failure, salvage surgery is probably

**TABLE 3: Clinical outcomes and GKS failure mode and timing**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>median clinical &amp; imaging FU in mos (range)</td>
<td>66 (26–121)</td>
</tr>
<tr>
<td>new permanent neurological deficit (%)</td>
<td>11 (50)</td>
</tr>
<tr>
<td>new trigeminal neuropathy (%)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>worst/most recent HB grade (%)</td>
<td></td>
</tr>
<tr>
<td>I–II</td>
<td>19 (86)/20 (91)</td>
</tr>
<tr>
<td>III–VI</td>
<td>3 (14)/2 (9)</td>
</tr>
<tr>
<td>median time in mos to worst HB grade in 4 patients (range)</td>
<td>49 (11–90)</td>
</tr>
<tr>
<td>new permanent CN VII weakness (%)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>new temporary hemifacial spasm (%)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>pre-GKS/most recent AAO-HNS hearing class (%)</td>
<td></td>
</tr>
<tr>
<td>A/B</td>
<td>10 (45)/3 (14)†</td>
</tr>
<tr>
<td>C/D</td>
<td>12 (55)/19 (86)†</td>
</tr>
<tr>
<td>loss of useful hearing among 10 patients w/ serviceable hearing prior to GKS (%)</td>
<td>7 (70)</td>
</tr>
<tr>
<td>median time in mos to loss of useful hearing in 7 patients (range)</td>
<td>16 (6–37)</td>
</tr>
<tr>
<td>new ataxia (%)</td>
<td>5 (23)</td>
</tr>
<tr>
<td>new imbalance/vestibulopathy (%)</td>
<td>8 (36)</td>
</tr>
<tr>
<td>steroid therapy required (%)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>median duration of steroid therapy in wks (range)</td>
<td>12 (3–37)</td>
</tr>
<tr>
<td>GKS failure (%)</td>
<td>4 (18)</td>
</tr>
<tr>
<td>post-GKS resection required (%)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>median delay from GKS to resection in mos (range)</td>
<td>32 (14–90)</td>
</tr>
<tr>
<td>serial tumor growth (%)</td>
<td>4 (18)</td>
</tr>
<tr>
<td>post-GKS VP shunt required (%)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>median delay from GKS to VP shunting in mos (range)</td>
<td>6 (5.8–9)</td>
</tr>
<tr>
<td>death (%)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

* For those 3 patients who experienced new permanent facial weakness, the median decrement was 1 HB grade (range 1–5 grades). Three patients met multiple GKS failure criteria. The pre-GKS and most recent HB grade are not significantly different. See the text for GKS failure definition.
† p < 0.01 compared with pre-GKS.

Fig. 2. Actuarial tumor control curve for 22 patients with large VSs treated with GKS. The number of patients still at risk for tumor progression at each time point appears in parentheses.

Fig. 3. Actuarial curve illustrating the preservation of pre-GKS HB grade over time. The number of patients still at risk for suffering facial weakness at each time point appears in parentheses.
more difficult and associated with increased CN morbidity.12,17,22,31

Establishing the aggregate tumor control rate after the resection of larger VSs is difficult because the large surgical studies have not documented radiographic follow-up beyond 1 year.1,21 Whatever the stated goal for the extent of resection, surgical series of large VSs often report outcomes for subgroups that ultimately undergo GTR/NTR, intended STR, or STR after resection is halted out of concern for morbidity (usually facial nerve dysfunction). Combining data from multiple studies that have evaluated recurrence after the resection of large VSs, the estimated recurrence rate following GTR is 2.8% (1 of 36 tumors), following NTR is 2.8% (2 of 71 tumors), and following STR is 32.1% (18 of 56 tumors).3,13,28,32 The aggregate reported tumor control rate after surgery alone is 87% (185 of 229 tumors). Without actuarial data, comparison with the 82% 5-year PFS reported here after GKS is not possible but probably similar over this follow-up period.

**Facial Nerve Preservation**

Facial and trigeminal neuropathy rates following GKS for small- to medium-sized VSs have dropped to <1% and 3%, respectively, with contemporary margin dosing (12–13 Gy).3,14,23 Tumor size, tumor margin dose, and prior resection are known risk factors for post-GKS facial weakness.4,8 In this series of larger tumors, 20 (95%) of 21 patients maintained pre-GKS HB Grade I–II at the time of the last follow-up, findings similar to those in another recent series.40 By comparison, in surgical series of VSs larger than 2.6 cm, excellent facial nerve function was preserved in 56%–91% of patients after GTR,1,13,16,28,35 in 86%–100%16,28,35 after planned STR, and in just 40%35 after resections halted at the STR stage due to CN monitoring changes (Table 4). While the number of patients in the present study is small, the rate of facial neuropathy after GKS for larger tumors is comparable with that after GKS for small- to medium-sized tumors and better than the rates reported following resection.

**Functional Hearing Preservation**

Functional hearing is considered an important goal after GKS for the treatment of small- or medium-sized tumors and can be attained in 50%–90%9,14,23 of patients. Factors that may influence hearing preservation after GKS include tumor size, tumor margin dose, and radiation dose to the cochlea.24 Hearing outcome often goes unreported in surgical series of larger VSs.1,13,28,33,35 In fact, the group at the House Research Institute (formerly the House Ear Institute) advocates the translabyrinthine approach for all large VSs regardless of preoperative cochlear function.21 The aggregate rate of functional hearing preservation from surgical studies reporting data for larger VSs is 13.1% (20 of 153 patients).6,7,11,16,32,36 The preservation of useful hearing after GKS for larger VSs is probably more common than after surgery for tumors of a similar size, although less common than after GKS for smaller tumors.

**Optimal Therapeutic Strategy**

The treatment of larger VSs is challenging. Patients

![Fig. 4. Actuarial curve demonstrating hearing preservation in 10 patients who had serviceable hearing (AAO-HNS Class A/B) before GKS to treat a larger VS. The number of patients still at risk for suffering hearing loss at each time point appears in parentheses.](image-url)
frequently present with mild symptoms from posterior fossa mass effect and a large or enlarging tumor. Limited data exist to support recommending surgery and/or radiosurgery. Gamma Knife surgery is nearly noninvasive and has excellent efficacy and limited morbidity, at least for small- or medium-sized tumors. Attempting curative resection of larger VSs can be associated with significant neurological morbidity. Deliberate STR seems to lower neurological risk, but nearly one-third of patients will harbor an enlarging residual tumor that requires additional treatment. The current study demonstrates a lower tumor control rate and a higher rate of CN morbidity for larger tumors than are historically reported for small- to medium-sized VSs treated with GKS (Table 4). However, CN morbidity after GKS is better than that usually reported after surgery for larger VSs. Hasegawa and colleagues described 1 large VS probably undergoing malignant degeneration 51 months after radiosurgery, similar to our case, raising some concern that tumor size may be a risk factor for this most dreaded complication.

We still recommend resection for the majority of patients with large VSs. For patients with a contraindication to microsurgery, GKS for larger VSs may be an alternative that balances tumor control and CN morbidity. A strategy of planned STR followed by GKS for an enlarging residual tumor may represent the optimal strategy, provided that the tumor volume can be safely reduced to create an acceptable radiosurgical target.\(^\text{13,16,28}\)

**Conclusions**

Single-session radiosurgery is a successful treatment for the majority of patients with larger VSs. However, tumor control is less than that achieved for small- or medium-sized tumors. The CN morbidity of GKS is lower than that achieved using open surgery for larger VSs.

**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: Link, Pollock. Acquisition of data: Link, Milligan. Analysis and interpretation of data: all authors. Drafting the article: Milligan. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Link. Statistical analysis: Milligan. Study supervision: Link.

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