

# Long-term outcomes of Gamma Knife radiosurgery in patients with vestibular schwannomas

## Clinical article

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**Object.** The authors sought to determine the long-term tumor control and side effects of Gamma Knife radiosurgery (GKRS) in patients with vestibular schwannomas (VS).

**Methods.** One hundred seventeen patients with VS underwent GKRS between January 1997 and February 2003. At the time of analysis, at least 5 years had passed since GKRS in all patients. The mean patient age was 60.9 years. The mean maximal tumor diameter was  $1.77 \pm 0.71$  cm. The mean tumor volume was  $1.95 \pm 2.42$  ml. Eighty-two percent of lesions received 1300 cGy and 14% received 1200 cGy. The median dose homogeneity ratio was 1.97 and the median dose conformality ratio was 1.78. Follow-up included MR imaging or CT scanning approximately every 6–12 months. Rates of progression to surgery were calculated using the Kaplan-Meier method.

**Results.** Of the 117 patients in whom data were analyzed, 103 had follow-up MR or CT images and 14 patients were lost to follow-up. Fifty-three percent of patients had stable tumors and 37.9% had a radiographically documented response. Imaging-documented tumor progression was present in 8 patients (7.8%), but in 3 of these the lesion eventually stabilized. Only 5 patients required a neurosurgical intervention. The estimated 1-, 3-, and 5-year rates of progression to surgery were 1, 4.6, and 8.9%, respectively. One patient (1%) developed trigeminal neuropathy, 4 patients (5%) developed permanent facial neuropathy, 3 patients (4%) reported vertigo, and 7 patients (18%) had new gait imbalance following GKRS.

**Conclusions.** Gamma Knife radiosurgery results in excellent local control rates with minimal toxicity for patients with VS. The authors recommend standardized follow-up to gain a better understanding of the long-term effects of GKRS. (DOI: 10.3171/2009.12.JNS091339)

**KEY WORDS** • Gamma Knife • vestibular schwannoma •  
radiosurgery • acoustic neuroma • cranial neuropathy • quality of life

**V**ESTIBULAR schwannomas are benign tumors involving the nerve sheath of CN VIII. The reported incidence of VS in the US is 2000–3000 per year, accounting for 5–10% of all intracranial tumors diagnosed in adults. These tumors are slow growing, with a growth rate ranging from 0 to 1.9 mm per year.<sup>5,8,33</sup> Despite the relatively slow growth of these tumors, a proportion of patients can present with debilitating symptoms, including neuropathies of CNs V, VII, and VIII. Because significant symptomatic improvement is often not achieved with either resection or radiation therapy, patients often opt for the less invasive choice.<sup>10,32</sup> Of the

radiotherapy choices, patients with smaller tumors often choose single-session SRS over fractionated radiation therapy or multisession radiosurgery because of the convenience of a 1-day, outpatient procedure.

In Sweden in June 1969, Leksell<sup>18</sup> undertook GKRS in his first patient with a VS. It is now widely accepted that for patients with small- to medium-sized tumors, SRS can provide effective rates of tumor control, on the order of 91–100% (Table 1).<sup>3,4,7,9–11,14,16,23</sup> Pollock and colleagues<sup>29</sup> compared the outcomes of microsurgery with radiosurgery for tumors smaller than 3 cm in diameter and found that radiosurgery provided more favorable results for facial function, hearing preservation, treatment-related morbidity, length of hospital stay, cost, and faster return to independent functioning. Although there was debate over this early report of radiosurgery, with follow-up of 5–15 years, the benefit of radiosurgery has been validated for appropriate-sized VS.<sup>3,4,7,9–11,14,16,23</sup>

*Abbreviations used in this paper:* CN = cranial nerve; DHI = Dizziness Handicap Inventory; GKRS = Gamma Knife radiosurgery; IRB = internal review board; LOS = length of stay; QOL = quality of life; PFS = progression-free survival; SRS = stereotactic radiosurgery; VP = ventriculoperitoneal; VS = vestibular schwannoma.

TABLE 1: Comparison of results from long-term studies of VS treated with radiosurgery\*

Authors & Year	Follow-Up (yrs)	No. of Patients	Mean Tumor Vol (cm <sup>3</sup> /D)/cm	Marginal Dose (Gy)	Mean IDL (%)	PFS (%)	Preservation (%)		
							CN V	CN VII	Hearing
Kondziolka et al., 1998†	5–10	162	NA/2.2	16.6 (mean)	50	98 (5-yr) 98 (10-yr)	73	73	51
Chopra et al., 2007	5.7	216	1.3/NA	13 (median)	50	98.3 (10-yr)	94.9	100	44
Hasegawa et al., 2005	>5	317	5.6/NA	13.2 (mean)	51	93 (5-yr)† 92 (10-yr)†	96 (>13 Gy); 98 (≤13 Gy)	94 (>13 Gy); 99 (≤13 Gy)	13 (>13 Gy); 68 (≤13 Gy)
Hasegawa et al., 2005	11.25	73	6.3/NA	14.6 (mean)	52	87 (10-yr)‡	92	89	68
Combs et al., 2006	9	26	NA/1.5	13 (median)	80	91 (5-yr) 91 (10-yr)	92	95¶	55
Iwai et al., 2008	7.4	25	0.27/NA	12	50	100 (5-yr) 100 (10-yr)	100	100§	64
Fukuoka et al., 2009	≥5	152	2.0/NA	12 (median)	NA	94 (5-yr) 92.4 (8-yr)	97.4	100	71
Kalogeridi et al., 2009	4.6	19	5.95/NA	11–12**	54	100††	100	100	NA
Myrseth et al., 2005	>3 to 4	103	NA	12.2 (mean)	NA	93‡‡	NA	94.8	32¶¶
present series	3.6	103	1.95/1.77	13 (median)	50	91.1 (5-yr)	99	95§§	NA

\* D = diameter; IDL = prescription isodose line; NA = not applicable.

† Progression-free survival with 9% of patients requiring a second intervention.

‡ Ninety-three percent for patients with tumor volume < 10 cm<sup>3</sup>.

¶ An additional 15% of patients had transient facial neuropathy.

§ One patient (4%) had transient facial neuropathy.

\*\* Linear accelerator-based radiosurgery.

†† PFS with follow-up of 55 months.

‡‡ Including 5 patients who underwent microsurgical resection and 2 patients who required VP shunt placement for symptomatic hydrocephalus.

¶¶ Ten of 31 patients maintained Gardner-Robertson Grade A and B hearing.

§§ An additional 5% of patients had transient facial neuropathy.

Patients with GKRS-treated VS must be followed up for several years to determine the true recurrence rates. Hasegawa and colleagues<sup>10</sup> reported 10-year results obtained in 73 patients treated with GKRS for VS and found that patients with good tumor control after 5 years did not experience tumor recurrence or require additional treatment. The same group reported that treatment failure typically presented within 3 years of treatment.<sup>9</sup> With regard to late side effects, Kondziolka and associates<sup>16</sup> reported that no new neurological deficits were seen beyond 28 months after radiosurgery. Thus, we believed that reporting outcomes of patients at least 5 years after GKRS was a reasonable time point to assess both treatment response and side effects.

## Methods

### Patient Characteristics

Using an IRB-approved GKRS VS database at Cleveland Clinic, we identified 117 patients with GKRS-treated VS between January 1997 and February 2003. The median patient age was 60.9 years (range 21–84 years). The patients included 56 men (49%) and 59 women (51%). Fifty-eight percent of tumors were on the right side. One patient (0.85%) had Type 2 neurofibromatosis. In 19 patients (16%) previous resection had failed, and 98 patients (84%) received GKRS as initial treatment. All but 7 pa-

tients had one or more presenting symptoms, which included hearing loss, unsteady gait, tinnitus, vertigo, facial neuropathy, trigeminal neuropathy, and ear pain or fullness. Most patients (72%) did not have useful ipsilateral hearing at the time of initial assessment and therefore did not undergo hearing evaluations prior to GKRS. Eleven patients (12%) had some degree of facial nerve dysfunction at presentation.

### Tumor Characteristics

Patients were considered candidates for GKRS if their maximal tumor diameter was ≤ 3 cm. The mean maximal tumor dimension was 1.77 ± 0.71 cm, and the mean tumor volume was 1.95 ± 2.42 cm<sup>3</sup>. Only 4 patients had tumors confined to the internal auditory canal, and the remaining 113 had tumors involving the cerebellopontine angle.

### Radiosurgery Technique

All patients were treated with the Leksell Gamma Knife Model B (Elekta) until March of 2002 when the machine was upgraded to a Leksell Gamma Knife Model C. The Leksell stereotactic frame was secured to the patients' skulls with the use of intravenous anxiolysis and local anesthetic. High-resolution 1.5-T MR images (Siemens AG) were acquired and 3D magnetization-prepared rapid gradient echo imaging with Gd contrast were collected over 1-mm slices with the head frame in place. A

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CT scan without contrast was also obtained to check for possible spatial distortions associated with the MR imaging. The neuroimaging studies were downloaded into the Gamma Plan stereotactic volumetric planning system and concordance between the CT and MR images was verified. The target volumes were then delineated by the neurosurgeon and verified by the radiation oncologist.

Optimized conformal treatment plans were generated by utilizing multiple isocenters. The mean number of isocenters was 4.75 (range 1–14). A majority of the tumors (82%) were prescribed 1300 cGy, and 14% received 1200 cGy. The mean maximum radiation dose was 2440 cGy (range 1630–2610 cGy), with 30% of patients receiving 2600 cGy as the maximum dose. The doses were prescribed to the 50% isodose line for most of the tumors, and 58% was the maximum prescription isodose line. No tumor was treated to less than the 50% isodose line. Sixty percent of the tumors had 100% coverage; 27% had 99% coverage and 13% had  $\geq 89$ –98% coverage. The median dose homogeneity ratio was 1.97, and the median dose conformality ratio was 1.78. The goal was to keep these ratios between 1 and 2. In a majority of cases, the eyes were shielded using manual plugging of the helmet.

### Follow-up Analysis

Serial contrast-enhanced MR imaging was conducted every 6 months for the first 2 years and annually thereafter. A CT scan of the head was acquired when MR imaging was contraindicated. If patients were not able to return for follow-up, they were asked to contact us with their imaging results. Imaging progression was defined as an increase by  $\geq 2$  mm in maximal tumor dimension, and response was defined as a decrease by  $\geq 2$  mm in maximal tumor dimension. Stable disease was defined as any change in imaging not meeting the criteria for progression or response.

### Statistical Analysis

Progression to surgery was the primary end point of this analysis. Surgery included microsurgical resection or placement of a VP shunt due to tumor growth. The need for surgery after GKRS was considered a GKRS failure. Patients who did not undergo surgery were censored at the date of their last follow-up MR imaging session. The Kaplan-Meier method was used to estimate time to progression. A descriptive analysis was performed of our secondary end points, which included imaging response, time to radiological response, presenting symptoms and response post-GKRS, new symptoms post-GKRS, and long-term evaluation of these symptoms. A dosimetric evaluation was performed on the plans of the patients requiring neurosurgical intervention.

## Results

All patients had completed GKRS at least 5 years prior to this analysis, but the range of follow-up varied from 3.2 to 116 months. The mean and median follow-up durations were 43.3 and 37.5 months, respectively. At the time of analysis, 106 patients were alive and no patients died of their VS or treatment-related complications.

There were no radiation-induced secondary malignancies or malignant transformations of the VS.

### Tumor Control and Response to Gamma Knife

Of the 117 patients analyzed, follow-up imaging was available for 103. At the time of last follow-up, 39 patients (37.8%) had a response and 55 patients (53.4%) had stable disease on imaging. The median time to response was 30.7 months (range 3.4–94.5 months). Eight (7.7%) of 103 patients had imaging evidence of progression; however, in 3 of these the tumor stabilized and/or reduced in size over time. The patient with Type 2 neurofibromatosis was more than 8 years out from GKRS at the time of analysis and had not required any additional interventions for the VS treated with GKRS. Regarding the 4 patients with tumor confined to the internal auditory canal, 2 had stable tumors and 2 had tumors that decreased in size.

Five patients required neurosurgical intervention (Table 2). The median time to neurosurgical intervention was 32.5 months (range 5.7–46 months). The median maximal dimension and tumor volume for these patients was 1.7 cm (range 1.59–2.33 cm) and 0.52 cm<sup>3</sup> (range 0.14–3.10 cm<sup>3</sup>), respectively. Four patients underwent neurosurgical intervention for progression of the VS. The 5th patient initially had VS growth noted at 4 months after GKRS and the VS continued to grow through 21 months. After this point, the size of the VS remained stable, but the patient developed communicating hydrocephalus and required VP shunt placement at 32.5 months post-GKRS. The estimated 1-, 3-, and 5-year rates of progression to surgery were 1, 4.6, and 8.9%, respectively (Fig. 1).

### Clinical Side Effects

Side effects were recorded as subjectively reported by patients along with the physical examination findings at each 6-month follow-up. Ninety-two patients had clinical follow-up data at the time of analysis. At each visit the patients underwent a detailed review of neurological complaints, including changes in hearing, tinnitus, facial weakness, facial numbness and/or paresthesia, gait imbalance, and vertigo. Changes in neurological symptoms after GKRS are illustrated in Table 3. The majority of patients who did not initially present with symptoms did not develop side effects following GKRS. Patients presenting with tumor-related neurological deficits prior to GKRS had a mixed response, with patients most likely to have stable or improved deficits, except for the patients with hearing loss.

Of the 26 patients who presented with useful hearing, 22 retained useful hearing and 4 patients reported new hearing loss. A majority (76%) of the patients with pre-treatment hearing loss reported no change in their ability to hear; 9% improved and 15% experienced progressive hearing loss.

One patient (1%) developed symptoms of trigeminal neuropathy following GKRS, which was associated with tumor progression. This patient had undergone a subtotal resection of the VS approximately 1.5 years before GKRS and underwent a salvage gross-total resection 31.6 months after GKRS.

TABLE 2: Patients requiring neurosurgical intervention following GKRS for VS\*

Case No.	Age (yrs)	Prior Resection	Tumor Vol at SRS	Dose (Gy)	No. of Isocenters	Tumor Coverage (%)	MD/PD	PIV/TV (cm <sup>3</sup> )	Time to Surgery (mos)	Intervention	Reason for Intervention
3	42	no	3.10	13	5	89	NA	0.97	46	GTR	growth of VS
53	80	no	0.47	13	9	100	1.95	1.95	32.5	VP shunt	comm hydro, growth of VS
71	53	no	0.14	13	2	98	1.72	1.87	5.7	GTR	growth of VS
82	54	no	2.60	13	6	100	2.0	1.54	46	STR	growth of VS
112	56	yes	0.52	13	2	100	2.0	2.9	31.6	GTR	growth of VS

\* comm hydro = communicating hydrocephalus; GTR = gross-total resection; MD/PD = maximum dose/prescription dose; PIV/TV = prescription isodose volume/tumor volume; STR = subtotal resection; TTS = time to surgery.

Facial nerve dysfunction was present in 11 patients at diagnosis. Eight patients developed facial nerve dysfunction after GKRS. Half of these patients with new facial neuropathy experienced transient symptoms that eventually improved to baseline status. Table 4 provides a summary of cases involving facial neuropathy.

Additional complications included dry eye in 1 patient. Five patients reported new headaches, with 1 patient developing this symptom less than 6 months from GKRS, 2 developing headaches after 6 months, and 2 at unknown times. Three patients reported transient nausea and vomiting after GKRS.

## Discussion

The primary goals in treating patients with VS are tumor control and maintaining QOL while minimizing treatment side effects. Stereotactic radiosurgery is a treatment modality that typically fulfills these goals. The Gamma Knife is successfully used throughout the world as a primary treatment modality for VS. Currently, salvage SRS is being investigated after failed primary radiosurgery. There are 2 reports of salvage radiosurgery demonstrating good tumor control outcomes with CN preservation similar to initial GKRS experiences.<sup>6,21</sup>

### Tumor Control

We report progression to surgery as the primary end

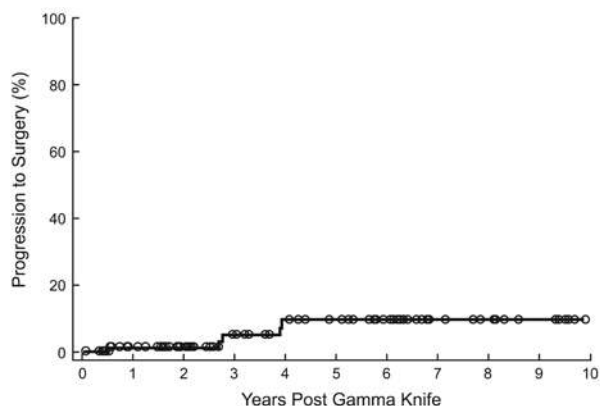


Fig. 1. Graph showing progression to surgery after GKRS.

point of our analysis. We believe that this end point represents the most important outcome by which to assess tumor control. Assessing radiographic outcomes remains important for our understanding VS response to GKRS. However, radiographic control can be a misleading end point: patients may exhibit radiographic progression without symptomatic progression and therefore never require additional intervention.

Although it is difficult to compare the results of multiple institutions, local control, as measured by freedom from surgical intervention, in long-term radiosurgery experiences is in the range of 91–100% for smaller tumors (Table 1).<sup>3,4,7,9–11,14,16</sup>

The mean size of tumors treated varies dramatically across institutions, from 0.27 to 6.3 cm<sup>3</sup>.<sup>3,4,7,9–11,14,16</sup> The size of the tumor has been a known prognostic factor for local control following GKRS. Hasegawa et al.<sup>10</sup> reported their long-term analysis of patients with VS treated with GKRS and found that tumor volume, number of isocenters, tumor type, and prior treatment significantly affected PFS. However, only tumor volume remained a significant predictor of PFS on multivariate analysis. Their actuarial 10-year PFS rate was 87% overall, but it was 93% in patients with tumors smaller than 10 cm<sup>3</sup>. Despite the various tumor sizes treated by these institutions, local tumor control remains excellent across all institutions. These high rates of tumor control should not be compromised by alternative means of radiation delivery and should be considered the standard of care.

### Salvage Treatments After GKRS

In the publication by Hasegawa et al.,<sup>9</sup> the median interval between GKRS and second treatment for the 27 patients (9%) requiring further treatment was 30 months, with a range of 3–52 months to craniotomy after GKRS. Others have reported a similar median of 37 months to the time of resection in patients with persistent or increasing symptoms.<sup>2</sup> At 32.5 months in our study, the median time to salvage surgery was comparable. Of the 8 patients with imaging progression, the tumor stabilized without further intervention in 3. Imaging progression in these patients was thought to be a reactive process following GKRS. These patients are now at the 7-, 8-, and 12-year mark

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**TABLE 3: Effects of GKRS on symptoms\***

Side Effect	Asymptomatic Prior to GKRS		Symptomatic Prior to GKRS		
	Preserved Function	Developed Dysfunction	Stable Dysfunction	Improved Dysfunction	Progressed Dysfunction
trigeminal neuropathy	89 (99)	1 (1)	3 (100)		
tinnitus	33 (80)	8 (20)	28 (55)	20 (39)	3 (6)
gait disturbance	31 (82)	7 (18)	21 (44)	20 (42)	7 (15)
vertigo	66 (96)	3 (4)	4 (17)	14 (61)	5 (22)
auditory neuropathy	22 (85)	4 (15)	50 (76)	6 (9)	10 (15)
facial neuropathy	70 (90)	8 (10)	8 (73)	2 (18)	1 (9)

\* Tabular values reflect the number of patients and, in parentheses, corresponding percentages.

after GKRS. Therefore, the decision to perform salvage surgery should be carefully considered. If the patient's symptoms allow, an appropriate duration of observation should be upheld.

At 91.1%, our freedom from progression to surgery at 5 years is comparable with that of other series. We have reported a detailed description of the 5 patients who required neurosurgical intervention (Table 2). After careful review of treatment plans of these 5 patients, it appears that in 3 patients, there was no clear deviation that might predispose to failure. In Case 3 in Table 2, in our attempt at a highly conformal plan the percentage of tumor coverage was only 89%. We have since modified the treatment guidelines to limit minimum allowable tumor coverage to 97% of the prescribed dose. For the patient in Case 71, we noted a 2–3-mm medial to lateral and cranial caudal shift between MR images and CT scans, which may have led to decreased tumor coverage (Fig. 2). The conformality and homogeneity indices did not correlate with the need for neurosurgical intervention; however, they do speak to the quality of the GKRS plan. The range of isocenters for these 5 patients varied between 2 and 9, making it difficult to correlate the number of isocenters with failure. However, recent reports in the literature suggest that increasing numbers of isocenters correlates with GKRS failure.<sup>28</sup> We will continue to gather this information as an indicator of the quality of treatment plans.

Gamma Knife radiosurgery in the patient in Case 53 (Table 2) was considered a failure due to the need for placing a VP shunt for symptomatic communicating hydrocephalus. This patient falls into a small group of VS patients in whom communicating hydrocephalus develops after GKRS. From an early experience, the Pittsburgh group reported 4% of their VS patients treated with GKRS developed communicating hydrocephalus and required VP shunts.<sup>20,22</sup> The mechanism of action is not clearly defined, but reports in the literature suggest that the necrotic tumor causes increased concentration of proteins in the CSF that lead to decreased resorption of the fluid.<sup>1,26</sup> Studies have shown that the increase in CSF proteins temporally correlates with the decrease in central enhancement of the tumor on imaging.<sup>26</sup> The communicating hydrocephalus caused by the increased CSF protein is typically seen at 1–2 years after GKRS.<sup>26,35</sup> Our patient had growth of the VS, followed by stabilization for 1 year, prior to the development of communicating

hydrocephalus 32.5 months after GKRS (Fig. 3). In this patient there was radiological evidence of necrosis (Fig. 3C). We hypothesize that this patient's communicating hydrocephalus was related to tumor necrosis caused by GKRS.

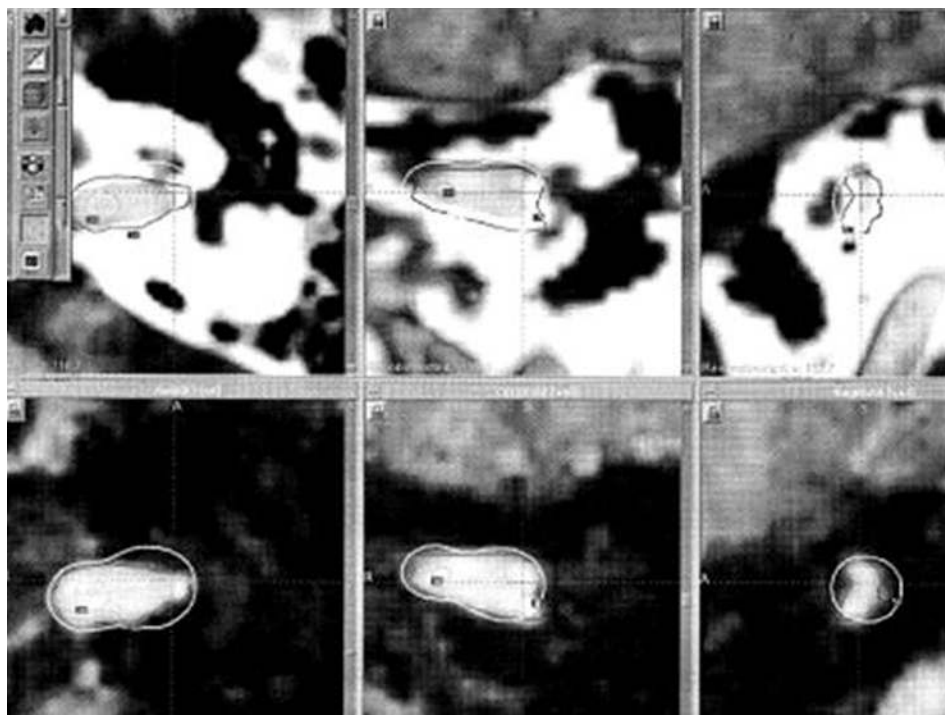
### Quality of Life

Assessing the differences in QOL outcomes between radiosurgery and microsurgery has been performed using generalized questionnaires, questionnaires specific to vestibular symptoms, standard cranial neuropathy assessments, and parameters such as LOS and days away from work.<sup>25,27,30,36,37</sup> Despite the variety of assessment tools, the results consistently point to radiosurgery as the treatment of choice for small tumors. Patient questionnaires are a proven tool to evaluate the patients' perceptions of their outcomes. Myrseth et al.<sup>25</sup> provided 2 general QOL questionnaires—the Glasgow Benefit Inventory and the Medical Outcomes Study 36-Item Short Form (SF-36)—to 186 consecutively treated patients with VS who had undergone either microsurgery or GKRS. Reduced QOL scores were identified in both treatments, but occurred

**TABLE 4: Patients in whom facial neuropathy developed after GKRS\***

Case No.	Mos Post-GKRS to Reported Side Effect	House-Brackmann Grade	Weakness Resolved	Pertinent Detail
20	6	II	no	NS
42	5	III	no	improved to Grade II
43	16.1	II	no	previous facial weakness after resection for the VS prior to GKRS
67	9.3	II	yes	NS
83	14.2	II	yes	NS
86	4.1	II	yes	previous resection prior to GKRS
89	6.9	III	yes	likely related to recurrence of Ramsey Hunt syndrome
91	9.6	III	no	required partial surgical closure of eyelid

\* NS = none specified.

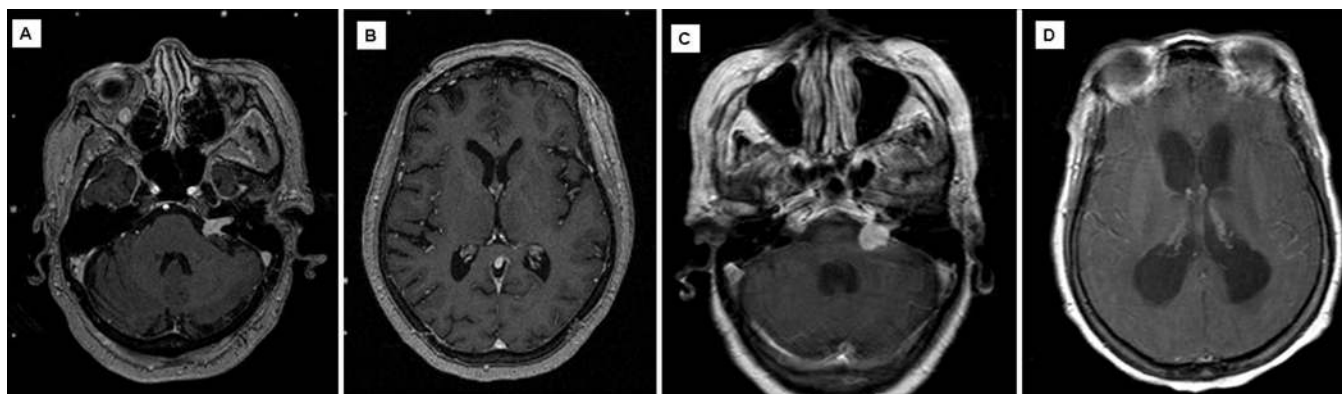


**Fig. 2.** Gamma Knife plan obtained in a patient requiring neurosurgical intervention. **Upper:** Images show the tumor contours projected on CT scans. **Lower:** Images illustrate the tumor volume as contoured on the axial Gd-enhanced MR images. Although it is difficult to see, there is a 2–3-mm shift in the medial to lateral and cranial to caudal direction when the MR imaging contours are compared to the CT-rendered anatomy.

to a larger degree in the microsurgery group. Similar results were demonstrated by the Pollock group.<sup>27</sup> They performed a prospective cohort study of patients with unilateral VS smaller than 3 cm treated with resection or radiosurgery, with a mean follow-up of 42 months. These patients were provided a DHI, tinnitus survey, headache survey, and Health Status Questionnaire. The patients had similar tumor and symptom characteristics, except that the patients in the radiosurgery group tended to be older. The results showed that normal facial movement and preservation of serviceable hearing were more frequent

in the radiosurgical group at 3 months, 1 year, and at the last follow-up. The surgery-treated patients fared significantly worse with regard to the DHI at the last follow-up and had a significant decline in several categories of the Health Status Questionnaire. Thus, the analysis points to radiosurgery as the preferred option.

Quality of life can also be assessed by the number of days that patients are able to perform activities of daily living. Regis et al.<sup>30</sup> performed a prospective evaluation of patients with VS who underwent microsurgery or GKRS. The authors found the mean LOS and the mean time away



**Fig. 3.** Axial Gd-enhanced T1-weighted MR images obtained in a patient in whom communicating hydrocephalus developed after GKRS. **A and B:** Images obtained the after the GKRS. **C:** Image acquired 32.5 months after GKRS. Enlargement and central necrosis are demonstrated in the posttreatment tumor. **D:** Image obtained 32.5 months after GKRS demonstrating ventriculomegaly.

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from work favored the radiosurgery group with 3 days of hospital stay and 7 days away from work compared with a hospital stay of 23 days and 130 days away from work in the microsurgery group.<sup>30</sup> It is important to note that these LOSs are exceptionally long compared with contemporary LOSs in the US because most centers send patients home the same day as the radiosurgical procedure.

In a group of 386 surgically treated patients with VS who completed the SF-36 and the DHI, 155 patients (40.15%) reported having a “really disabling symptom” including hearing loss, dysequilibrium, facial dysfunction, tinnitus, headache, or eye problems following the procedure.<sup>36</sup> The authors also reported that overall, 84.5% were able to return to work. Only 9.1% of patients were able to carry out daily activities after more than 3 weeks, whereas 3–6 weeks of recovery were required in 21.7% of patients, 3–6 months in 27.8% of patients, and more than 6 months in 23.8%.

### *Treatment Side Effects*

The most prominent side effects associated with treatment of VS include auditory, trigeminal, and facial neuropathies. The Pittsburgh group has reported significant rates of facial weakness (21%), facial numbness (27%), and decreased hearing (49%) in their first 5 years of experience with VS radiosurgery when using marginal tumor doses of 16 Gy.<sup>16</sup> These high complication rates led to a decrease of the prescription dose to 12 or 13 Gy. This reduction in dose resulted in improved 10-year actuarial preservation of facial and trigeminal nerve functions of 100 and 94.9%, respectively.<sup>3</sup> Similarly, Hasegawa and colleagues<sup>9</sup> have reported a 1% rate of developing transient facial weakness and 2% rate of developing facial numbness in patients in whom a marginal dose of 13 Gy or less was prescribed. A meta-analysis of 2204 patients with VS treated with GKRS reported facial nerve preservation to be significantly different when the prescription dose was  $\leq$  13 Gy (98.5%) compared with  $>$  13 Gy (94.7%).<sup>37</sup> Other factors found to be significant for facial nerve preservation included tumors  $\leq$  1.5 cm<sup>3</sup> and patient age  $\leq$  60 years.

We have reported the results of linear accelerator-based SRS (median dose 16 Gy to the periphery) in patients with VS.<sup>34</sup> The long-term complications included new or progressive trigeminal and facial nerve deficits with estimated 5-year incidences of 15 and 32%, respectively. Despite excellent local control, we recommended against CT-only-based planning and high peripheral doses to the tumor. We began prescribing 12–13 Gy to the margin when we started our GKRS program in 1997, using both MR imaging- and CT-based planning. Our results with this program have been comparable to other single-institution experiences except for our 90% preservation rate of the facial nerve. Half of these patients experienced resolution of their symptoms within several months, providing a 95% long-term preservation rate of the facial nerve. Two of the patients in our series had surgery prior to GKRS and this likely increased their risk of facial nerve dysfunction.

### *Future Directions*

As our planning techniques become more sophisti-

cated, we may develop dosimetric parameters to assist with evaluating the dose to the cochlea, facial nerve, and trigeminal nerve as higher doses to these structures may compromise function. There are several reports in the literature correlating a specific dose to the cochlea, with preservation of hearing a cutoff dose to the cochlea ranging from  $<$  3.7 Gy to  $<$  4.75 Gy.<sup>15,17,19,24,31</sup> In addition to dose, attention should be given to patient factors such as previous surgery, presenting symptoms, age, and comorbidities when assessing CN function.

Our current dose conformality and homogeneity ratios do not correlate with neurosurgery-free survival, imaging response, or preservation of CN function. However, prospective evaluations of dosimetric parameters, conformality and homogeneity ratios, and the number of isocenters should be analyzed in reference to tumor control and CN symptoms and will enhance outcome assessment.

Implementing a standardized VS treatment protocol would improve the utility of reported data. One deficiency of our program had been the lack of standardized evaluations pre- and post-GKRS. Our patient population consisted of older patients without useful hearing at presentation. Increasing age has been shown to be negatively prognostic for hearing preservation and therefore we would not expect much improvement in our specific patient population.<sup>15,31</sup> However, in more recent years, we have routinely evaluated patient hearing pre- and post-treatment.

In addition to hearing evaluations, it is important to assess the impact of tinnitus and dizziness on the lives of our patients. We have started to collect data using the Tinnitus Questionnaire and the DHI. The DHI was developed by Gary Jacobson as a self-administered 35-question instrument that reflects a patient's perception on the impact of dizziness on his or her QOL.<sup>12</sup> This index has been used for patients with VS treated with both resection and GKRS.<sup>27,30,36</sup> The DHI has been shown to correlate with specific balance function investigations.<sup>13</sup> We believe that it is appropriate to prospectively assess patients with both pre- and post-GKRS hearing evaluations and questionnaires to effectively evaluate this procedure (Table 5).

## Conclusions

Gamma Knife radiosurgery results in excellent local control rates with minimal toxicity for patients with VS. We recommend standardized assessment including hearing evaluations and patient questionnaires to enhance the understanding of the long-term effects of GKRS in this population. We look forward to evaluating specific dosimetric parameters that may correlate with patient outcomes and assist in optimizing GKRS treatment planning.

### Disclosure

Dr. Barnett is a speaker for Elekta, and Dr. Neyman is a consultant for Elekta. The authors declare that no additional actual or potential conflicts of interest exist.

The information provided in this manuscript is maintained in a Cleveland Clinic IRB-approved database (IRB No. 6988).

**TABLE 5: Proposed prospective patient evaluation protocol before and after GKRS\***

hearing evaluation (speech discrimination and pure tone average)
DHI
tinnitus questionnaire
contrast-enhanced MRI of the brain
photographic documentation of facial asymmetry

\* Post-Gamma Knife radiosurgery evaluations to be performed every 6 months for the first 1–2 years and annually thereafter.

Author contributions to the study and manuscript preparation include the following. Conception and design: JH Suh, ES Murphy, GH Barnett, MA Vogelbaum, G Neyman, GHJ Stevens, BH Cohen, P Elson, AD Vassil. Acquisition of data: ES Murphy, GH Barnett, MA Vogelbaum, G Neyman, GHJ Stevens, AD Vassil. Analysis and interpretation of data: JH Suh, ES Murphy, GH Barnett, G Neyman, GHJ Stevens, BH Cohen, P Elson. Drafting the article: JH Suh, ES Murphy. Critically revising the article: JH Suh, ES Murphy, GH Barnett, MA Vogelbaum, G Neyman, GHJ Stevens, BH Cohen, P Elson, AD Vassil. Reviewed final version of the manuscript and approved it for submission: JH Suh, ES Murphy, GH Barnett, MA Vogelbaum, G Neyman, GHJ Stevens, BH Cohen, P Elson, AD Vassil. Statistical analysis: ES Murphy, P Elson. Study supervision: JH Suh.

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Manuscript submitted September 10, 2009.

Accepted December 16, 2009.

Portions of this work were presented in abstract and poster form at the ASTRO Meeting, Boston, MA, September 21–25, 2008.

Please include this information when citing this paper: published online January 22, 2010; DOI: 10.3171/2009.12.JNS091339.

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