REPEAT GAMMA KNIFE SURGERY FOR REGROWTH OF VESTIBULAR SCHWANNOMAS

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OBJECTIVE: Gamma knife surgery (GKS) has become established as a minimally invasive treatment modality for patients with vestibular schwannomas. Treatment failure and/or tumor regrowth, however, is occasionally encountered, and microsurgical resection is usually warranted in such cases. The role of repeat GKS in these situations is still unclear. The goal of this study was to investigate whether repeat GKS is an effective treatment for recurrent vestibular schwannomas and to assess the conservation of residual neurological function.

METHODS: Between July 1992 and December 2007, 1951 patients harboring a unilateral vestibular schwannoma were treated with GKS. Of these, 48 patients (2.5%) had to undergo a subsequent intervention because of progression or regrowth of the tumor. Repeat GKS was performed in a total of 15 patients, 8 of whom had more than 2 years of follow-up and were eligible to be enrolled in the present study. The median follow-up period after repeat GKS was 64 months, and the median interval between these interventions was 46 months. The median tumor volume was 0.51 and 1.28 mL at the initial and second GKS treatments, respectively. Patients received a median prescription dose of 12.0 Gy at both interventions.

RESULTS: We report no cases of failure. Six patients demonstrated a significant reduction in tumor volume. In 1 patient, the final tumor volume was less than the initial volume. The other 2 patients showed stabilization of tumor growth. Useful hearing ability was preserved in only 1 of the 3 patients who had serviceable hearing ability at the time of the second GKS. Neither aggravation of facial nerve dysfunction nor other neurological deficits secondary to GKS were observed.

CONCLUSION: This is the first report to address repeat GKS for vestibular schwannomas. After long-term follow-up, repeat GKS with a low marginal dose seems to be a safe and effective treatment in selected patients harboring regrowth of small vestibular schwannomas that have previously been treated with GKS.

KEY WORDS: Acoustic neuroma, Gamma knife surgery, Hearing preservation, Radiosurgery, Recurrence, Vestibular schwannoma

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Over the past decade, the quality of gamma knife surgery (GKS) has increased as a result of improvements in imaging technology, chiefly in magnetic resonance imaging (MRI), and advances in radiosurgical technology, as well as the development of radiosurgical knowledge and skills (11–13, 27, 33, 37). Many investigators have reported that GKS is a safe and minimally invasive treatment modality for patients with vestibular schwannomas (VS) (4, 6, 9, 17, 20, 24–26, 28). Treatment failure and/or uncontrolled tumor regrowth after GKS, however, is encountered occasionally, and microsurgical excision is generally advised under these circumstances (2, 10, 16, 17, 24, 25, 30, 35). Some authors have reported specific difficulty with functional preservation during microsurgical removal of VSs that were previously treated by GKS (18, 19, 30, 32, 35). Recent articles have advocated subtotal tumor removal to maximize the chances of preservation of cranial nerve function (16, 24). Owing to the paucity

ABBREVIATIONS: GKS, gamma knife surgery; **MRI**, magnetic resonance imaging; **VS**, vestibular schwannoma

of literature on the methods and results of retreatment of VSs with GKS, it is still difficult to evaluate the potential role of repeat GKS in patients presenting with treatment failure more than 3 years after initial GKS. The goal of this study was to elucidate whether repeat GKS is an effective treatment for a recurrent VS and to assess the conservation of residual neurological function.

PATIENTS AND METHODS

Patient Characteristics

Between July 1992 and December 2007, 1951 consecutive patients presenting with a VS (excluding 95 patients with neurofibromatosis Type 2) were treated with GKS at Timone University Hospital in Marseille. Forty-eight patients (2.5%) had to undergo subsequent intervention because of progression or regrowth of their VS. Thirty-three patients underwent microsurgical resection, and 15 patients underwent repeat GKS. More than 24 months of follow-up data are available for 8 of the patients who underwent repeat GKS, and these patients were included in the present study (Table 1). No patient was lost to follow-up. The characteristics of the patients are shown in Table 2. The interval between the initial GKS and reintervention ranged from 35 to 99 months (median, 46 months). Facial nerve function and hearing were evaluated using House-Brackmann grading and Gardner-Robertson classification, respectively (7, 14). Gardner-Robertson Grades I and II were considered to be serviceable hearing. Seven patients who underwent GKS as an initial treatment had normal facial nerve function and serviceable hearing at the time of the first GKS. The other patient had already undergone 2 previous microsurgical resections before the first GKS and had complete hearing loss as well as severe facial palsy at the time of the first GKS.

TABLE 1. Summary of data on treatment of vestibular schwannomas in our center[a]

Variable	Value
Total no. of patients	2046
Non-NF2 patients, no.	1951
Treatment failure, no. (%)	48 (2.5 %)
Retreatment	48
Microsurgery	33
Repeated GKS	15
≤2005	8
2006–2007	7

[a] NF2, neurofibromatosis Type 2; GKS, gamma knife surgery. The treatment period was July 1992 to December 2007.

Indication for Repeat GKS

Results of the first GKS treatment for VS were evaluated after almost 3 years (3, 16, 40). On each follow-up MRI scan, the tumor volume was calculated from 6 length measurements, defined precisely by anatomic landmarks. Our methodology for assessment of MRI changes has been reported previously (3). We define treatment failure, according to Delsanti et al. (3), as continuous growth of the tumor at more than 3 years after GKS that needs subsequent intervention. Patients fulfilling the following criteria underwent repeat GKS: no new significant neurological deficit evident, tumor size less than Koos Grade IV (brainstem deformation), no major cystic component in the tumor, and consent of the patient to undergo radiosurgery in preference to microsurgery after full discussion of the treatment options.

Radiosurgical Techniques

GKS was performed using the Leksell G stereotactic frame (Elekta Instruments, Stockholm, Sweden). The frame was placed on the patient's head after induction of local anesthesia and with mild sedation. All patients underwent both stereotactic MRI and computed tomography. Since 1999, sequences of 3-dimensional constructive interference in steady state with and without gadolinium and 3-dimensional magnetization prepared rapid acquisition gradient echo with gadolinium have been used routinely. These imaging techniques could more clearly visualize the position of adjacent cranial nerves that were distorted by the tumor (11, 12). Until July 1997, the Kula system (Elekta Instruments) was used for dose planning; thereafter, GammaPlan software (Elekta Instruments) was introduced. At the end of the dose planning, spatial distortion of the MRI scans was evaluated meticulously and corrected for by comparing several MRI sequences as well as checking computed tomographic images against magnetic resonance images. The Leksell Model B gamma knife was used until May 2000 and was then replaced by the Model C, which allowed more selective and conformal dosimetry by using the Automatic Positioning System (Elekta Instruments) (27).

TABLE 2. Characteristics of 8 patients who underwent repeated gamma knife surgery[a]

Patient no.	Age (y)/sex	Side	Onset symptom	Pre-GKS treatment	Pre-GKS			Other symptoms
					Koos	G&R	H&B	
1	52/F	L	Incidental	MS ×2	2	5	5	Facial dysesthesia
2	58/M	R	Vertigo	None	1	2	1	None
3	76/F	L	Instability	None	2	1	1	None
4	52/F	R	Vertigo	None	2	1	1	None
5	51/F	R	Tinnitus	None	2	2	1	None
6	46/M	R	Decreased hearing	None	2	1	1	None
7	41/M	L	Decreased hearing	None	1	2	1	None
8	56/M	L	Decreased hearing	None	2	2	1	None

[a] GKS, gamma knife surgery; G&R, Gardner-Robertson classification; H&B, House-Brackmann grade; L, left; MS, microsurgical resection; R, right.

Follow-up Evaluation

Clinical follow-up data comprised the neuroradiological evaluation of MRI scans as well as an otoneurological evaluation including audiological tests and facial nerve function assessment. If patients lived at a great distance from our institution, we contacted the patients or their referring doctor by telephone to collect detailed clinical information. Tumor response to repeat GKS was classified into 4 categories according to tumor volume as follows: regression (more than 10% volume reduction as compared with the volume at the second GKS), stabilization (volume alteration within 10% of the volume), enlargement more than 10% volume increase not requiring subsequent intervention, failure (uncontrollable tumor growth requiring further intervention and/or appearance of disabling radiation side effect).

RESULTS

The median interval between these interventions was 46 months (range, 35–99 months), and the median follow-up period after repeat GKS was 64 months (range, 26–121 months). The oldest patient died from unrelated causes at 92 months after repeat GKS. The median tumor volume at the first intervention was 0.51 mL (range, 0.10–1.40 mL). At the repeat GKS, the median tumor volume was 1.28 mL (range, 0.54–3.07 mL). The median tumor volume ratio (volume at the subsequent GKS to volume at the first GKS) was 2.9 (range, 1.4–5.2). The median annual growth rate was calculated as 60% per year (range, 12–87% per year). The median marginal prescription dose was 12.0 Gy (range, 12–14 Gy) for the initial GKS and 12.0 Gy (range, 10–12 Gy) for the repeat GKS. The median isodose line for the target volume was 50% (range, 40–50%) for the initial GKS and 50% (range, 45–50%) for the repeat GKS (Table 3).

At the time of last follow-up, 6 patients were in the regression category of treatment response, and 2 were in the stabilization category; none of the patients experienced enlargement or failure. In 2 patients (Patients 1 and 3), the tumor volume at the last follow-up was carefully evaluated by reference to examination reports by neuroradiologists in their region. The radiological report on Patient 1 stated that the tumor had decreased in size from 23 × 12 mm to 20 × 9 mm, and the report for Patient 3 stated that the tumor was stabilized and comparable to its form at the second GKS. Concerning the other 6 patients, the final median tumor volume was 0.60 mL—i.e., 213% of the volume at the first treatment and 65% of the volume at the second treatment. The MRI for the patient with the longest follow-up after repeat GKS (Patient 2) is illustrated in Figure 1. There were no other abnormal neuroradiological findings, such as cerebellar edema or hydrocephalus (Table 4).

At the time of the second intervention, 3 of 7 patients with conserved useful hearing at the first GKS still had useful hearing. Of these 3 patients, only 1 patient ultimately had preservation of serviceable hearing at the time of the 26-month follow-up evaluation after repeat GKS.

In all 7 patients with normal facial nerve function at the first treatment, neither permanent nor transient facial nerve dysfunction was observed throughout this study. No other neurological deficits considered as secondary effects of GKS were encountered. Apart from 1 patient who died of an unrelated cause, all 7 patients maintained their performance status at the preoperative level.

DISCUSSION

GKS for VS has been considered a valuable treatment option since the 1990s. Many investigators have reported long-term efficacy and low procedural complication rates (4, 6, 9, 17, 20, 24–26, 28). In modern series, treatment failures are rare, occurring in less than 5% of cases (5, 15, 23, 26, 29). However, the management of failure and/or tumor regrowth is an important issue (2, 10, 16, 17, 24, 25, 30, 35). Microsurgical resection is an established treatment option for a growing VS after GKS, although rates of preservation of cranial nerve function with this procedure vary widely (16, 18, 19, 24, 30, 32, 35). In our institution, the majority of patients with tumor regrowth were treated microsurgically (30). With the aim of maximal functional preservation, we performed the second GKS only when the aforementioned criteria were strictly fulfilled.

TABLE 3. Operative technique and radiological results of 8 patients with repeated gamma knife surgery[a]

Patient no.	1st GKS		Annual growth rate (%/y)	2nd GKS		FU interval after 2nd GKS (mo)	Treatment results	TV reduction (%)	Radiological complications
	TV (mL)	Peripheral dose (Gy)		TV (mL)	Peripheral dose (Gy)				
1	1095	14	12	1536	12	106	Regression	−35	None
2	104	12	78	542	12	121	Regression	−58	None
3	1092	12	62	3072	10	92	Stabilization	0	None
4	495	14	21	824	10	80	Regression	−51	None
5	203	12	58	802	12	35	Regression	−32	None
6	1400	12	14	3003	12	26	Stabilization	−4	None
7	528	12	87	2496	11	26	Regression	−17	None
8	334	12	73	1032	12	49	Regression	−37	None

[a] GKS, gamma knife surgery; TV, tumor volume; FU, follow-up.

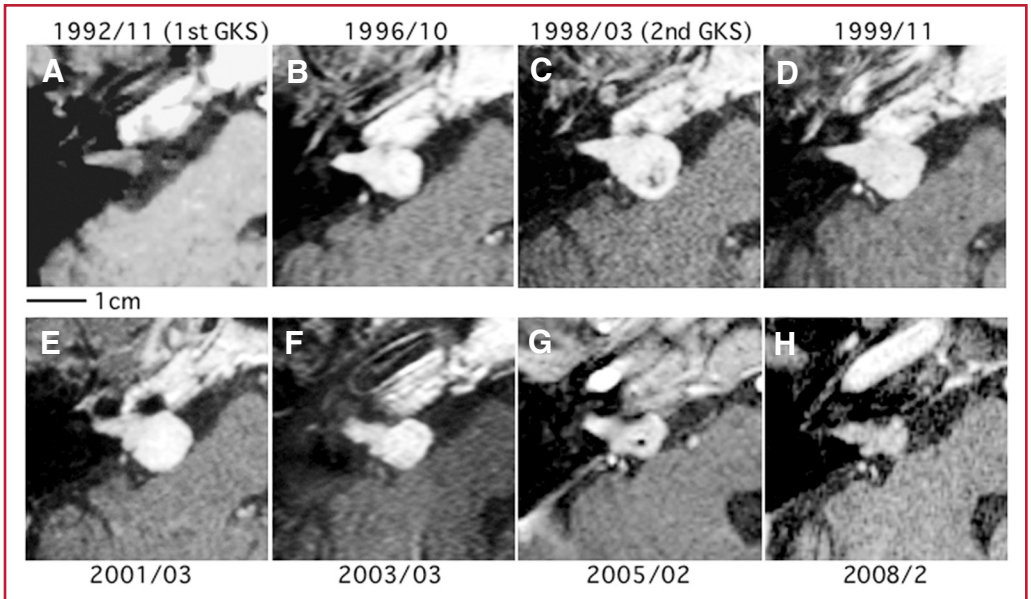

FIGURE 1. *Patient 2, a 58-year-old man with a right vestibular schwannoma (VS), who was followed for the longest follow-up period after repeat gamma knife surgery (GKS).* **A–H**, *serial magnetic resonance imaging (MRI) scans obtained from 1992 to 2008.* **A**, *MRI scan, 1992. The tumor volume at the initial GKS (peripheral dose, 12 Gy) was 0.1 mL. The tumor continued to grow (***B***), and the patient underwent repeat GKS (peripheral dose, 12 Gy) (***C***) 64 months after the first intervention when the tumor volume was 0.54 mL. Tumor regression was continuous (***D–G***). The tumor volume was calculated as 0.23 mL at the last follow-up examination (121 months) (***H***).*

Treatment Indications

It is crucial to select patients who are eligible candidates for repeat GKS treatment. In fact, the selection criteria are very similar, in our opinion, to those for first GKS treatment. Our follow-up protocol is to evaluate treatment results for almost 3 years after GKS unless the patient develops significant cerebellar ataxia or pyramidal tract signs before that time. If such symptoms are caused by tumor growth, we routinely perform or recommend microsurgical resection for immediate symptom relief. Consequently, only small-volume tumors (median, 1.28 mL) were included in the present study.

Detailed clinical and radiological information at the time of intervention was available for 24 of 31 patients who underwent subsequent microsurgical resection during the same study period. We compared this population with the population of the present series (Table 5). This demographic comparison revealed that the only significant difference between these 2 populations was the size of the tumor at the time of the decision (tumors were smaller in patients selected for repeat radiosurgery).

Tumor Control

The median tumor volume at the last examination was significantly smaller than at the time of the second GKS in 6 of the 8 patients, although it was still larger than the volume at the first GKS (Table 3). In only 1 case was the tumor volume after repeat GKS smaller than at the time of the first intervention (Fig. 2). Some may consider that these results are insufficient to affirm the effect of repeat GKS. However, before the second treatment, the median tumor growth rate was 60% per year, which is much higher than the natural course of an ordinary VS (31, 34, 38, 39). Complete cessation of tumor growth in such circumstances is, for us, a very clear demonstration of the efficacy of repeat GKS. We also found a tendency for the tumor shrinkage rate to be higher in patients with a longer follow-up interval after the second intervention. This continuous tumor volume reduction after retreatment supports the long-term efficacy of repeat GKS, although careful

TABLE 4. Neurological results of 8 patients with repeated gamma knife surgery[a]

Patient no.	1st GKS		Treatment interval (mo)	2nd GKS		FU interval (mo)	Last FU		Neurological complications
	G&R	H&B		G&R	H&B		G&R	H&B	
1	5	5	40	5	5	106	5	5	None
2	2	1	64	2	1	121	4	1	None
3	1	1	35	2	1	92	4	1	None
4	1	1	37	3	1	80	4	1	None
5	2	1	62	3	1	35	3	1	None
6	1	1	99	3	1	26	2	1	None
7	2	1	51	2	1	26	4	1	None
8	2	1	34	3	1	49	3	1	None

[a] GKS, gamma knife surgery; G&R, Gardner-Robertson classification; H&B, House-Brackmann grade; FU, follow-up.

TABLE 5. Comparison of the populations with repeated GKS and microsurgical resection[a]

Variable	2nd GKS	Microsurgery	*P* value
No. of patients	8	24	
Median age at 1st GKS (y)	52	51	0.654[b]
Sex (female:male)	4:4	12:12	0.657[c]
Previous microsurgical resection	1	1	0.444[c]
Median treatment interval (mo)	46	40	0.586[b]
Median initial TV (mL)	512	1232	0.063[b]
Median TV at subsequent intervention (mL)	1284	4916	0.002[b]
Median tumor growth (%)	293	329	0.623[b]
Median tumor growth rate (%/y)	60	54	0.685[b]

[a] GKS, gamma knife surgery; TV, tumor volume.
[b] Mann-Whitney test.
[c] Fisher's exact probability test.

long-term follow-up is mandatory. In our series, the follow-up interval after repeat GKS ranges from 26 to 121 months.

Hearing Preservation

Seven patients had serviceable hearing before initial GKS, and 3 of these patients still had useful hearing at the time of repeat GKS. At the time of the last follow-up evaluation, only 1 patient maintained useful hearing ability (Table 4). The other 4 patients retained perceptible hearing. None of the patients became completely deaf. The median follow-up time from the first GKS in the present study was 121 months. The results of repeat GKS in terms of hearing preservation appear to be poor.

Annual hearing deterioration rate after each intervention was calculated for all patients except for Patient 1, who had complete deafness, by using the pure tone average (Fig. 3). The median hearing deterioration rate after the first GKS and the second GKS was 3.2 dB per year (range, 0–8.4 dB per year) and 6.9 dB per year (range, 2.6–8.5 dB per year), respectively. Repeat GKS seemed to accelerate hearing deterioration; however, this difference was not statistically significant (Wilcoxon matched-pairs signed-rank test, $P = 0.469$). Accumulated dose to the cochlea might have contributed to hearing impairment (36).

According to the literature on the conservative treatment of acoustic neuromas, hearing ability would be expected to decline by 2.4 to 5.1 dB per year on average (1, 8, 21, 38). Therefore, it is difficult to draw any conclusions regarding any deleterious effect of repeat GKS on hearing, as the results may simply reflect the natural history. It remains unclear whether gradual worsening of hearing ability after repeat GKS is attributable to the biomechanical effect of the tumor itself or to the side effects of radiation. The risk of hearing loss after the second GKS seems to be higher than after the first GKS. For a patient failing to respond to a first GKS, however, we believe that a second GKS is still advantageous, compared with microsurgery, in terms of preservation of cranial nerve function.

Other Neurological Complications

It is noteworthy that we encountered no facial nerve functional deterioration attributable to repeat GKS (Table 4). Several investigators have reported high efficacy and low morbidity of low-dose treatment for VSs (5, 15, 22, 23); therefore, we have consistently adopted a comparatively low-dose treatment strategy aimed at maximal functional preservation. The median time interval between the 2 interventions in the present study was 46 months. The combination of low-dose treatment and the fact that the median interval between treatments was almost 4 years could theoretically have worked in favor of protection of facial nerve function. Considering that no other adverse effects, such as cerebellar ataxia, have been observed thus far in this small population, it would seem reasonable

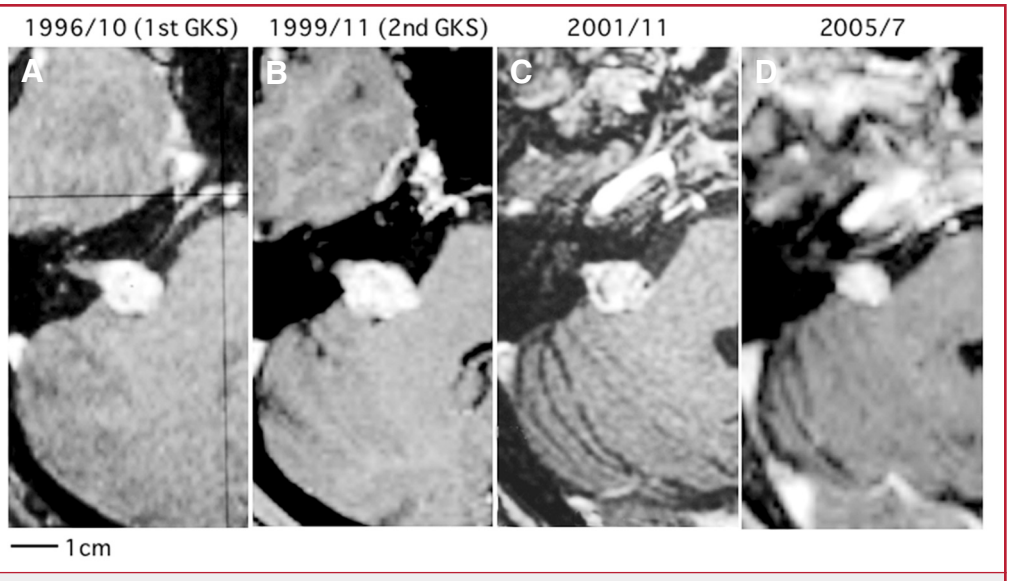

FIGURE 2. *Patient 4, a 52-year-old woman with a right VS.* **A–D**, *serial MRI scans obtained from 1996 to 2005. The patient underwent the first GKS in 1996 (***A***). The second GKS was performed 37 months later because of tumor enlargement (***B***).* **C** *and* **D**, *MRI scans showing consistent tumor regression at 36 months (***C***) and 68 months (***D***) after repeat GKS.*

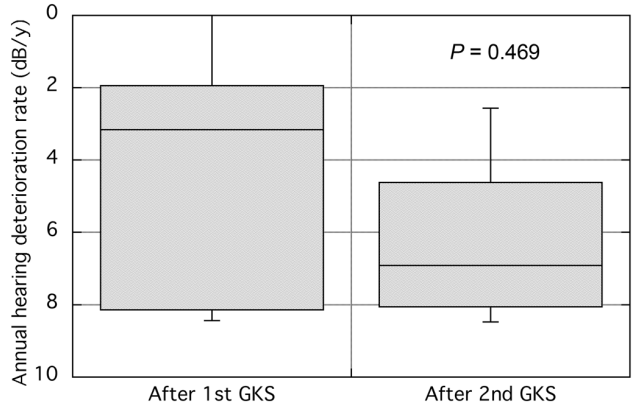

FIGURE 3. *Bar graph showing annual hearing deterioration rate (dB per year). Median values after the first and second GKS were 3.2 dB per year (range, 0–8.4 dB per year) and 6.9 dB per year (range, 2.6–8.5 dB per year), respectively. Repeat GKS seemed to accelerate hearing deterioration; however, this difference was not statistically significant (Wilcoxon matched-pairs signed-rank test, P = 0.469).*

to advocate repeat GKS as a safe approach, particularly for small, recurrent VSs.

The aims of treatment of a VS are to achieve long-term tumor control and to preserve residual neurological function. Therefore, we suggest that repeat GKS is a feasible treatment option for appropriately selected patients in whom the first GKS failed.

CONCLUSIONS

After long-term follow-up, repeat low-dose GKS has been demonstrated to be an effective alternative to microsurgical resection in selected patients harboring regrowth of small VSs. None of the patients developed facial nerve dysfunction or any other neurological complication, although the functional hearing preservation rate was poor. To the best of our knowledge, this is the first report to address the issue of repeat GKS for VSs.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

In most large series with extended follow-up, gamma knife radiosurgery has been effective in providing tumor control and eliminating the need for additional management in 97 to 98% of patients. Thus, some tumors do progressively enlarge and require further care. The definition of "enlargement" can be debated, but if several scans, over 1 to 2 years, show progressive growth (not temporary expansion of the capsule), then either a second radiosurgery or resection is the usual option. In this study, Yomo et al. obtained good results in 8 patients who underwent a second radiosurgery. Unfortunately, they do not provide the outcomes in the 24 patients who underwent a resection.

We have performed a second radiosurgery in a small group of patients, typically with smaller tumors that have enlarged but are still fairly small. We used a margin dose of 10 or 11 Gy in most of these patients and similarly found subsequent tumor regression. The procedure has been safe. Although the data remain small, it appears that repeat radiosurgery in properly selected patients can be an effective strategy for patients who did not desire a resection in the first place.

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This is a very important article on a controversial topic. In every major study on vestibular schwannoma (VS) radiosurgery, it has been shown that many patients will demonstrate tumor enlargement after the procedure. The decision as to when and how to intervene for these patients remains a point of great contention. The majority of VS patients will have a volumetric increase during the first year after radiosurgery and a loss of central tumor enhancement; this is almost always a temporary expansion, and later imaging reveals a decrease in tumor size (1, 2). Approximately 5% of VSs expand after radiosurgery but do not show progressive enlargement, which would be indicative of failure. However, a small percentage of VS patients (2.5% in the current series) fail radiosurgery, and further tumor-directed therapy is indicated. To interpret the findings as failure, as defined by the Marseille group (continuous growth of the tumor at 3 or more years after radiosurgery), requires a complete and mature understanding of the imaging changes encountered after radiosurgery. In this series, the median time to repeat radiosurgery was almost 4 years, reinforcing the concept that impulsive decisions are rarely needed for these slow-growing, benign tumors.

Nonetheless, once it has been determined that radiosurgery has failed, what should be the recommended treatment? If the growth pattern after radiosurgery is primarily related to the enlargement or development of a cyst, then surgical resection is usually the best course of action (1). Yet, because experienced VS surgeons have reported that VS resection in patients who have undergone prior radiosurgery is more difficult and the incidence of facial weakness greater when compared with the incidence in patients who have not undergone radiosurgery, exploring other treatment options for VS patients whose tumor morphology is solid seems sensible. In this study, all 8 patients having repeat VS radiosurgery showed either a reduction in tumor volume (n = 6) or no change in tumor size (n = 2) at a median of 64 months. Of note, the median prescribed dose was the same as at the initial procedure (12 Gy), and no patient experienced additional facial weakness. We have had 1 patient with an enlarging tumor who underwent stereotactic radiation therapy (30 Gy in 10 fractions) after failed radiosurgery as an alternative to surgical resection. Five years later, the tumor is smaller, and she continues to have normal facial movement, so this also may be an option for this patient group. This is a significant contribution that will aid in the management of VS patients after radiosurgery.

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The article by Yomo et al. is an important addition to the results of treatment for VSs that recur after prior radiosurgery. As the authors point out, a recurrence requiring subsequent treatment after initial radiosurgery is an infrequent event, occurring in only 2.5% of their patients (excluding those with neurofibromatosis Type 2). Most of these recurrences were managed by microsurgical removal, but the smaller ones, as in this study, were managed with repeat radiosurgery. Many clinicians worry about the cumulative toxicity and neurological morbidity of repeat radiosurgery, but this article proves otherwise. Although the rate of hearing deterioration was more rapid after second radiosurgery, there was no case of transient or permanent worsening of facial nerve function and no other neurological morbidity.

Experienced surgeons know that transient enlargement of vestibular schwannomas occurs after radiosurgery and that, when

this happens in the first 2 years after treatment, careful, close follow-up usually proves the best course. For those tumors that require surgery within the first few years, it is reported that preservation of hearing and good facial nerve function is less likely. My experience with operating on only 2 cases that failed, with cystic enlargement, was that dissection of the solid tumor from the facial nerve was no different than if the patient had never been treated. Both were small intracanalicular tumors at initial radiosurgery, so the volumes of irradiation were small. This study confirms that repeat radiosurgery worsens hearing outcome but does not appear to affect facial nerve function. Since radiation may be "a gift that keeps on giving," it will be interesting to read about even later follow-up on facial function in another few years' time.

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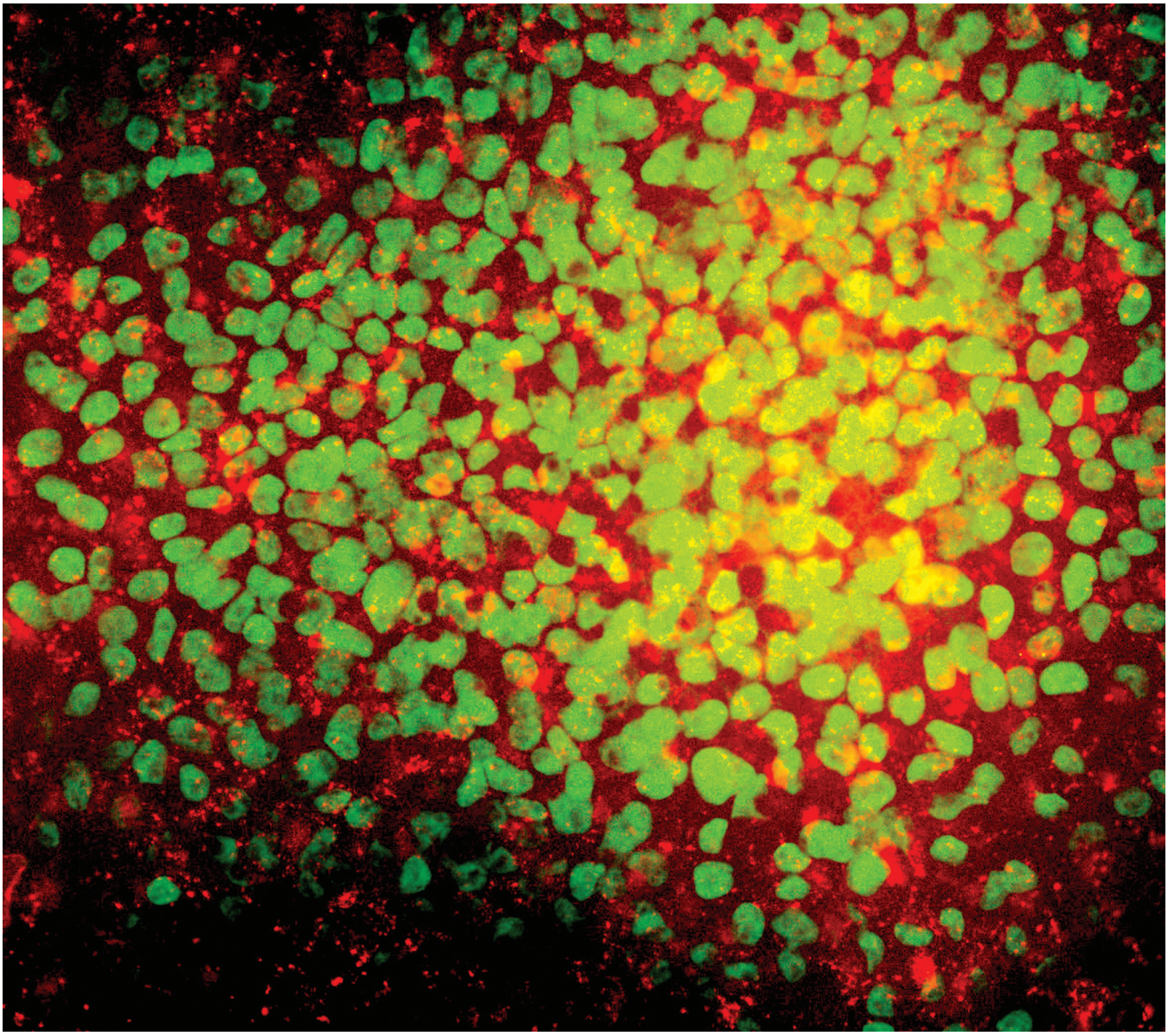

Human embryonic stem cells stained with two stem cell markers, SSEA3 (red) and sox2 (green). Credit: Rick Cohen, Ph.D., W.M. Keck Center for Collaborative Neuroscience, Rutgers, the State University of New Jersey. See Apuzzo, p 1, and Farin et al., pp 15–39.