

Original Article

Repeat Gamma Knife surgery for vestibular schwannomas

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Abstract**Background:** Gamma Knife (GK) surgery is a recognized treatment option for the management of small to medium-sized vestibular schwannoma (VS) associated with high-tumor control and low morbidity. When a radiosurgical treatment fails to stop tumor growth, repeat GK surgery can be proposed in selected cases.**Methods:** A series of 27 GK retreatments was performed in 25 patients with VS; 2 patients underwent three procedures. The median time interval between GK treatments was 45 months. The median margin dose used for the first, second, and third GK treatments was 12 Gy, 12 Gy, and 14 Gy, respectively. Six patients (4 patients for the second irradiation and 2 patients for the third irradiation) with partial tumor regrowth were treated only on the growing part of the tumor using a median margin dose of 13 Gy. The median tumor volume was 0.9, 2.3, and 0.7 cc for the first, second, and third treatments, respectively. Stereotactic positron emission tomography (PET) guidance was used for dose planning in 6 cases.**Results:** Mean follow-up duration was 46 months (range 24–110). At the last follow-up, 85% of schwannomas were controlled. The tumor volume decreased, remained unchanged, or increased after retreatment in 15, 8, and 4 cases, respectively. Four patients had PET during follow-up, and all showed a significant metabolic decrease of the tumor. Hearing was not preserved after retreatment in any patients. New facial or trigeminal palsy did not occur after retreatment.**Conclusions:** Our results support the long-term efficacy and low morbidity of repeat GK treatment for selected patients with tumor growth after initial treatment.**Key Words:** Acoustic neuroma, Gamma Knife, irradiation, radiosurgery, recurrence, regrowth, retreatment, vestibular schwannoma

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**INTRODUCTION**

Gamma Knife (GK) surgery has become a recognized treatment option for the management of small to medium-sized vestibular schwannoma (VS). The treatment aims to achieve long-term tumor control and to preserve the function of cranial nerves. Using low prescription doses, GK treatment offers high-tumor control with low morbidity.^[6] However, GK irradiation sometimes fails to stop tumor growth in the long-term.^[10]

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For such patients, microsurgical resection of the VS is generally advised. The tumor removal remains associated with difficulty to preserve cranial nerve function with a risk of hearing loss, facial palsy, facial numbness, and other surgical morbidity. This has led some authors to advocate repeat GK surgery instead of microsurgery or in combination with partial or subtotal tumor resection for these patients.^[3,7,9,18] However, the results of repeat GK irradiation for VS that continue to grow after prior GK surgery are not well established. In the present study, we analyzed the outcome of a series of 27 retreatments by GK surgery for VS.

MATERIALS AND METHODS

The present study was approved by the local institutional review board of the Ethical Committee of ULB - Hôpital Erasme (ref. P2015/207). Informed consent was obtained.

Indication for repeat Gamma Knife surgery

We performed a retrospective analysis of the clinical and radiological data for a series of patients treated radiosurgically more than once for the same VS in our department. After the first GK procedure, all these patients were followed up regularly by serial magnetic resonance imaging (MRI) and clinical evaluations in our clinic. A transient tumor volume increase after irradiation occurred occasionally and was not considered as tumor growth from failed GK surgery. Treatment failure was defined as a significant growth of a part or the entire tumor volume after a minimum period of 18 months with an increased growth rate after this period, possibly associated with worsening of cranial nerve function. In fact that the tumor growth rate increased after the usual period of transient volume expansion following GK irradiation was a major criterion to determine the failure of previous treatment. Repeat GK surgery was performed in patients with the following criteria: Previous GK treatment failure as defined above, no significant brainstem deviation due to excessive tumor size, no cystic component into the tumor, and patient preference to undergo new GK rather than microsurgery after full discussion of both treatment options. Three patients had microsurgical removal of a part of the tumor before GK retreatment.

Radiosurgery technique

Detailed information on the benefits and risks of GK retreatment was provided and discussed specifically for all patients according to their particular medical situation. All patients gave informed consent for new GK treatment. Preoperative evaluations, treatment procedures, and follow-up examinations were performed in accordance with the ethical standards of the Belgian Committee on human experimentation and with the Helsinki Declaration.

All patients underwent a radiosurgical procedure with the Leksell GK C (from July 2004 to September 2005), 4C (from September 2004 to June 2010), or Perfexion (from July 2010). The Leksell G stereotactic frame was applied to the patient's head under local anesthesia with mild intravenous sedation. For all patients, we performed MRI to acquire stereotactic axial three-dimensional (3D) gadolinium-enhanced T1-weighted and T2-weighted sequences, followed by a computed tomography (CT) densitometric scan. For retreatment, 6 patients also underwent a stereotactic positron emission tomography (PET) acquisition with methionine as the radiotracer, providing a set of 63 planes with a slice thickness of 2.4 mm for dose planning.^[8] The use of PET images provide additional information on the metabolic activity of the tumor that can help to optimize the dosimetry.^[8] Treatment planning was achieved using Leksell GammaPlan software (Elekta, Stockholm, Sweden). A target volume was drawn according to the tumor visualized on T1 and T2 MR-sequences and according to osseous limits of the internal auditory canal visualized on the CT-scan. When PET images were available, we checked that tumor hypermetabolic activity was included in the final target volume. A highly conformational radiosurgical planning was achieved by outlining the target with multiple isocenters of the same or different diameters to cover the entire tumor volume with the prescription isodose. The dose plan was transferred to the operating console of the Leksell GK and treatment was delivered with robotized stereotactic positioning of the patient's head. The stereotactic frame was removed immediately after irradiation. Patients were discharged the same day or the day after treatment.

Patient follow-up

Follow-up evaluations were scheduled every 6 months for the 1st year, and annually thereafter if the patient's condition was stable, and tumor volume remained unchanged or reduced on MRI. When the tumor increased, MRI was performed at 6-month intervals. Evolution of the tumor volume was assessed on MRIs co-registered on the follow-up module of Leksell GammaPlan 9.0. This module allows fusion of co-registered images in 3D and projection of the contours of the target volume and prescription isodose in follow-up images. Several volume measurements, as well as accurate evaluation of local or global tumor growth, can be performed with this advanced software. Tumor response was classified into three categories according to tumor volume as follows: Decreased volume (more than 10% volume reduction as compared to the volume at the last GK treatment), stable volume (volume variation within 10% of the volume at the last GK treatment), and increased volume (more than 10% volume enlargement as compared to the volume at the last GK treatment). Tumor metabolic response on PET-methionine was assessed by

variations in a semi-quantitative metabolic scale from 0 to 3: 0 = hypometabolic, 1 = isometabolic, 2 = moderately hypermetabolic, and 3 = very hypermetabolic, as compared to normal brain parenchyma.

RESULTS

Patient characteristics

We analyzed data from a series of 27 GK treatments carried out in 25 patients (13 women and 12 men) treated more than once for the same VS in our GK center between 2004 and 2013 [Table 1]. Twenty-three patients underwent two GK procedures and 2 patients underwent three GK procedures. All patients were followed up for a minimum of 2 years after their last GK treatment. We treated by GK surgery a total of 728 patients with VS during the observation interval. The percentage of patients who required a second and a third procedure was 3.43% and 0.27%, respectively.

The median age at the time of retreatment was 53 years (range 32–82). We treated 11 VS located on the left side and 14 VS located on the right side. Neurofibromatosis Type 2 disease was not present. Nine patients (36%) had tumor resection before the first GK irradiation and 3 patients had microsurgery after failure of the first radiosurgery treatment. The median time interval between GK treatments was 45 months (range 24–112). The indication for re-irradiation was global tumor regrowth for 21 retreatments and partial tumor regrowth for six retreatments. Patient hearing status was categorized by the Gardner-Robertson (GR) classification.^[5] At the time of retreatment, 13 patients had cophosis, 5 patients had a GR Grade 1–2 hearing level, and 9 patients had a GR Grade 3–4 hearing level. Four patients had facial nerve palsy before GK retreatment resulting from a previous microsurgical procedure in all cases. One patient had trigeminal nerve dysfunction (facial numbness) before the second GK procedure.

Table 1: Patients characteristics

Variable	Value
Total number of retreatments	27
Total number of patients	25
Patients with 2 GK treatments	23
Patients with 3 GK treatments	2
Age (years)	53 (32-82)
Gender (female/male)	13/12
Side (left/right)	11/14
Surgery before first GK irradiation	9
Surgery before repeat GK irradiation	3
Time interval to retreatment (months)	45 (24-112)
Reason for retreatment	
Global regrowth	21
Partial regrowth	6

GK: Gamma Knife

Dosimetric parameters

As shown in Table 2, the median margin dose used for the first GK treatment was 12 Gy (range 12–13), 12 Gy (range 11–15) for the second treatment, and 14 Gy (range 13–15) for the third treatment. Six patients (4 patients for the second irradiation and 2 patients for the third irradiation) with partial tumor regrowth were treated only on the growing part of the tumor using a median margin dose of 13 Gy (range 12–15). The median tumor volume was 0.9 cc (range 0.1–9.2) for the first GK treatment, 2.3 cc (range 0.2–8.3) for the second treatment, and 0.7 cc (range 0.2–1.1) for the third treatment. The median Paddick conformity index was 0.81 (range 0.63–0.92) for the first treatment, 0.85 (range 0.67–0.96) for the second treatment, and 0.70 (range 0.69–0.71) for the third treatment.^[16]

Tumor volume response of repeat Gamma Knife treatment

All patients were followed up clinically and radiologically for a minimum of 24 months after the last GK treatment. The mean follow-up duration was 46 months (range 24–110). No patient died during follow-up. At the last follow-up, 15 tumors had decreased in volume [Figures 1 and 2], 8 tumors remained unchanged, and 4 tumors had increased in volume [Table 3]. Thus, 85% of VS were controlled after re-irradiation. Two patients with increased global tumor volume after GK retreatment had microsurgical tumor resection, and 2 patients with the growth of part of the tumor were treated by a third GK procedure [Figure 3].

For 6 patients, the new GK treatment focused only on an area inside the tumor that showed local growth as the rest of the tumor did not grow. These patients had a favorable outcome with necrosis at the targeted volume and stopping of tumor growth [Figure 3].

Four of these 6 patients, retreated under stereotactic PET guidance [Figures 2 and 4], had PET examinations during follow-up. All patients showed decreased tumoral metabolic activity after re-irradiation, and all of them had tumor control on MRI.

Clinical outcome

A hearing test performed before the second GK surgery showed that 11 patients were deaf (GR Grade 5), 5 patients preserved useful hearing (GR Grade 1–2), and 9 patients preserved nonuseful hearing (GR Grade 3–4). Both patients treated by three GK procedures were deaf before the third irradiation. After retreatment, all patients were deaf [Table 4]. Two patients preserved nonuseful hearing, 5 patients worsened from useful hearing to nonuseful hearing, 2 patients preserved nonuseful hearing, and 7 patients worsened from nonuseful hearing to cophosis.

Four patients had facial paralysis before retreatment due to the initial microsurgery procedure performed before

Table 2: Radiosurgical technique

Parameter	Value
First GK treatment	
Margin dose (Gy)	12.0 (12-13)
Tumor volume (cc)	0.9 (0.1-9.2)
Paddick CI	0.81 (0.63-0.92)
Second GK treatment	
Margin dose (Gy)	12.0 (11-15)
Tumor volume (cc)	2.3 (0.2-8.3)
Paddick CI	0.85 (0.67-0.96)
Third GK treatment (2 patients)	
Margin dose (Gy)	14 (13-15)
Tumor volume (cc)	0.7 (0.2-1.1)
Paddick CI	0.70 (0.69-0.71)
Use of PET scan in dosimetry	6 patients

CI: Conformity index, PET: Positron emission tomography, GK: Gamma Knife

the first GK treatment. Of the 23 s or third GK irradiation procedures performed on patients with an initially normal nerve function, neither permanent nor transient facial nerve paresis was observed at the outcome. One patient had facial numbness before retreatment that remained unchanged during follow-up. All other patients had preserved normal trigeminal function after the second and third GK procedures. No other neurological deficit related to repeated GK surgery occurred.

DISCUSSION

GK surgery has emerged as an alternative therapeutic option for patients with VS. This treatment has been shown to be a valuable therapy with high, long-term efficacy, and low complication rates.^[6,10] However, even

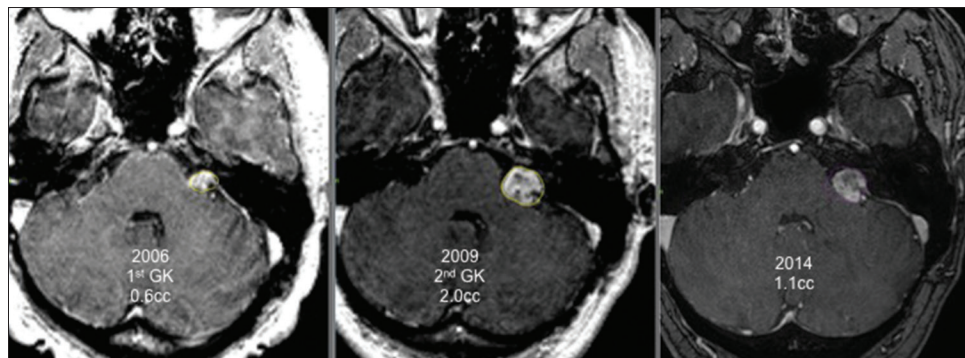


Figure 1: Left vestibular schwannoma, first Gamma Knife treatment in 2006 (0.6 cc), second treatment in 2009 (2.0 cc), and last control in 2014

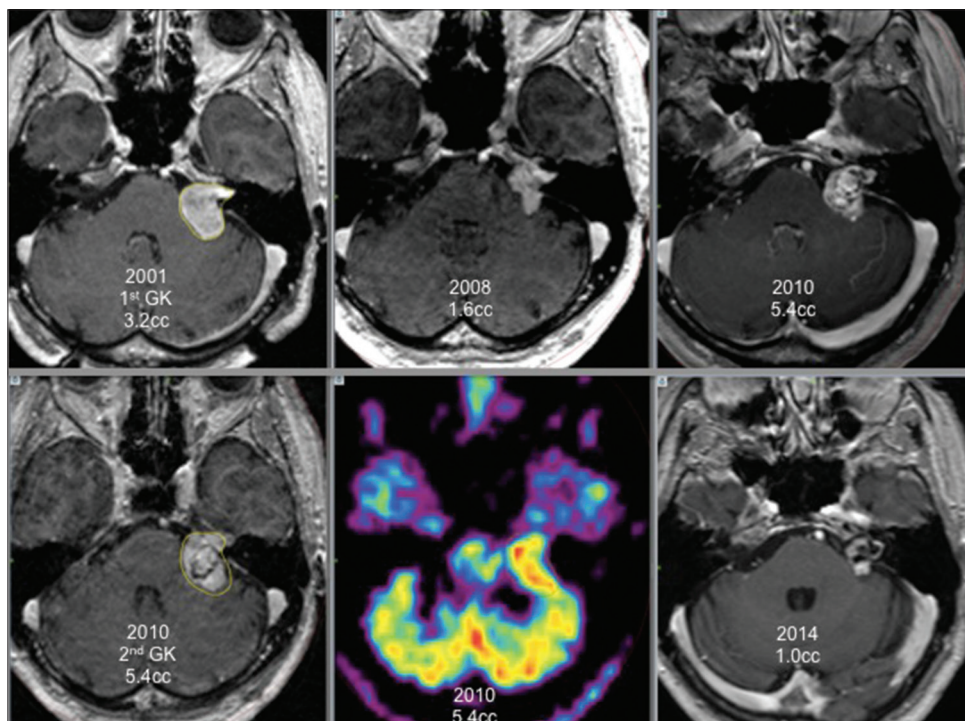


Figure 2: Left vestibular schwannoma, first Gamma Knife treatment in 2001 (3.2 cc), good initial response (1.6 cc in 2008), tumor regrowth in 2010 (5.4 cc), second Gamma Knife treatment in 2010 (5.4 cc) with positron emission tomography guidance, last control in 2014 (1.0 cc)

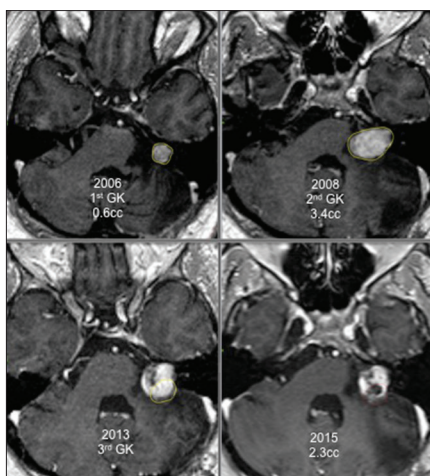


Figure 3: Left vestibular schwannoma (residue after surgery), first Gamma Knife treatment in 2006 (0.6 cc), second treatment in 2008 (3.4 cc), third treatment for local growth in 2013, and last control in 2015 (2.3 cc)

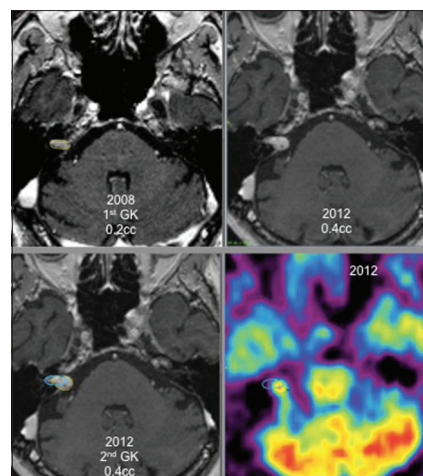


Figure 4: Right vestibular schwannoma, first Gamma Knife treatment in 2008 (0.2 cc), tumor growth in 2012, second treatment in 2012 (0.4 cc) with positron emission tomography guidance

Table 3: Radiological results

Variable	Value
Follow-up duration (months)	46 (24-110)
MRI	
Increased	4
Stable	8
Decreased	15
Tumor control	23 (85%)
PET	
Metabolic increased	0
Metabolic stable	0
Metabolic decreased	4

MRI: Magnetic resonance imaging, PET: Positron emission tomography

Table 4: Neurological results

Variable	Value
Follow-up duration (months)	46 (24-110)
Hearing preservation	
Deaf (grade 5) before retreatment	13
Preserved useful hearing (grade 1-2)	0
Preserved nonuseful hearing (grade 3-4)	2
Decreased to nonuseful hearing (grade 3-4)	5
Decreased to deaf (Grade 5)	7
Facial nerve dysfunction	
Facial dysfunction before retreatment	4
Preserved normal facial function	23
Worsening of facial function	0
Trigeminal nerve dysfunction	
Trigeminal numbness before retreatment	1
Preserved normal trigeminal function	26
Worsening of trigeminal function	0
Adverse radiation effects	
Transient edema	0
Permanent edema	0

if treatment failure is rare, the management of patients with tumor growth after radiosurgery remains a critical issue.^[17] Microsurgical resection is an established treatment option for growing VS after GK surgery. Yet, the preservation of cranial nerves function and avoidance of surgical complications remain challenging. Although a majority of patients with VS uncontrolled after GK treatment were operated, we performed a second or third GK irradiation in selected cases.

Indication for re-irradiation

Transient tumor expansion after GK radiosurgery for VS is a well-known phenomenon that has been reported in 17–74% of patients in different series.^[2,14,17] A transient tumor increase typically occurs between 3 and 9 months after irradiation with a peak observed usually at 6 months. The maximal tumor volume expansion averaged 47% in one large series.^[14] When treatment was successful, schwannomas shrank over a mean period of 12 months.^[17] More recently, Mindermann and Schlegel have found that transient tumor expansion occurred at about 6–18 months following GK surgery.^[13] New treatment should actually be reserved for patients with a tumor that continues to grow after this period. Progressive tumor volume enlargement can be accurately estimated by co-registration of serial imaging acquired during follow-up.^[17,19] The median time period between GK treatments of our patients was 45 months, which is similar to other series [Table 5].

For patients who require additional treatment after a failed first GK procedure, the selection criteria are very similar to those used for the first GK treatment. Surgical resection must be proposed for patients with large tumors that create symptoms due to a mass effect on the brainstem or other structures such as cerebellar ataxia or motor weakness.^[18] Cranial nerve function preservation after microsurgery remains challenging.

Table 5: Review of the literature

Author (references)	Year	Number of retreatments	Period	Mean dose to the first treatment	Mean dose to the second treatment	Size/volume of the first treatment	Size/volume of the second treatment	Time interval between treatments	Follow-up duration	Tumor control (%)	Useful hearing preservation	Facial nerve preservation (%)	Trigeminal nerve preservation (%)
Dewan and Norén ^[3]	2008	11	1994-2007	12 Gy	12 Gy	16.9 mm (9-30.6)	20.9 mm (13.5-33.4)	51 months (24-136)	-	91	1/1	11/11 (100)	9/11 (82)
Yomo <i>et al.</i> ^[17]	2008	8	1992-2007	12 Gy	12 Gy	0.51 cc	1.28 cc	46 months (35-99)	64 months (26-121)	100	1/7	7/7 (100)	8/8 (100)
Liscak <i>et al.</i> ^[8]	2009	24	1992-2001	12.5 Gy	13 Gy	1.1 cc (0.2-3.8)	2.9 cc (0.7-6.5)	43 months (12-125)	43 months (22-121)	92	2/2	18/19 (95)	22/24 (92)
Kano <i>et al.</i> ^[7]	2010	6	1987-2008	13 Gy	11.5 Gy	0.5 cc (0.1-2.3)	2.1 cc (0.9-6.4)	63 months (25-169)	29 months (13-71)	100	0/0	3/3 (100)	6/6 (100)
Present study	2015	27	2004-2013	12 Gy	12 Gy	0.9 cc (0.1-9.2)	2.3 cc (0.2-8.3)	45 months (24-112)	46 months (24-110)	85	0/5	23/23 (100)	26/26 (100)

The patients have to be aware of morbidity associated with microsurgical tumor removal and must accept it. Moreover, microsurgery might be inadvisable for some patients for the same reason that microsurgery was avoided in favor of the initial GK procedure.^[17] Surgery can lead to complete tumor removal or planned partial resection in order to reduce tumor volume followed by a new radiosurgical irradiation on the residual tumor. Repeat GK surgery can be proposed for patients with small to medium-sized tumors.

Few studies have reported the results of a second GK treatment for VS.^[3,7,9,18] Table 5 summarizes the data and outcome of these series. Liscak *et al.* published the largest study to date by reporting the results of 24 patients treated twice by GK surgery.^[9] Dosimetric parameters including tumor volumes and radiation doses on the first and second irradiations are similar to the parameters of our series.

Total versus partial re-irradiation

Our series included six GK re-treatments targeting only a part of the tumor. For these patients, thorough analysis of the tridimensional volumetric evolution of the schwannoma after radiosurgery showed clearly that only a part of the tumor was growing while the rest of the tumor volume was controlled by prior irradiation. We performed new GK treatment focused only to the growing area of the tumor to reduce the risks of the added radiation dose delivered to the cranial nerves and the brainstem. After a median follow-up of 42 months, all patients retreated with a new irradiation focused only on the growing part of the tumor had a significant reduction of the targeted volume and achieved whole tumor control.

Third Gamma Knife irradiation

Two patients were treated thrice with GK surgery. In both cases, the last irradiation was done only to the growing part of the tumor. An example of this state is provided in Figure 3. Since the growing part of the tumor to retreat was not in close proximity to the seventh and eighth cranial nerves, we prescribed radiation doses of 13 Gy and 15 Gy. Both patients had tumor control during their follow-up at 2.5 and 4.5 years after the last GK treatment.

Tumor control

In the efforts for facial and hearing preservation following GK surgery, the pioneers of GK treatment for VS have decreased gradually the prescription dose used. For almost 20 years, a reduced margin dose of 12 to 13 Gy is commonly used.^[1,4,6,15] This approach is associated with a significant reduction of the risks of worsening of cranial nerves function after treatment. In return, the use of lower radiation doses is associated to some extent with a reduced rate of long-term tumor control. Using the hypothesis that a higher radiation dose could stop tumor growth, a second GK irradiation for patients with tumor growth after GK treatment was proposed [Table 5].

Our results showed that for selected patients, new GK treatment for VS that continue to grow after a prior GK irradiation could be associated with a high rate of tumor control. We observed that 85% of the tumors retreated stopped growing after treatment and that 55% had a significant tumor volume reduction. To our knowledge, only four authors have reported the results of repeat GK treatment for growing VS [Table 5]. In a review of 24 patients who underwent two GK procedures for VS, Liscak *et al.* observed that 92% of tumors were controlled in the long-term.^[9] They have used same dosimetric and volumetric parameters as in our series. Dewan and Norén reported the results of 11 patients retreated with GK surgery for VS with no further tumor growth for 10 patients (91%).^[3] Small groups of 8 and 6 patients have also been reported by Yomo *et al.* and Kano *et al.*^[7,18] Both series provide excellent results with tumor control after the second GK treatment for all patients.

Functional outcome

In our experience, the results of hearing outcome after repeat GK treatment were poor. Five patients with useful hearing were retreated, but none of them retained serviceable hearing during follow-up. However, half of the noncophotic patients who underwent re-irradiation had a GR 3 hearing level at the last control. Repeat GK surgery seems to accelerate hearing deterioration. The accumulated radiation dose delivered to the cochlea or intracanalicular part of the tumor might have contributed to hearing impairment.^[11,12]

Functional preservation of the facial nerve represented one of the most critical challenges of GK retreatments. None of the 23 retreatments performed on patients with the prior normal function of the seventh cranial nerve induced any facial paralysis, even partial, or transient. One case of facial worsening after a second GK irradiation of VS was reported by Liscak *et al.*^[9] They performed treatments with a GK device that did not provide robotized positioning of the stereotactic coordinates during treatment and was associated with less precision in the delivery of radiation dose at the target than current GK treatments performed with GK C, 4C, or Perfexion. For the first irradiation as for retreatments of the whole tumor volume, we consistently adopted a low-dose treatment strategy aimed at the maximal chances of functional preservation of the seventh cranial nerve. The median time interval of 45 months between treatments in our series could also have played a role in the maintenance of facial nerve function after a second or third GK irradiation.

One of our patients had facial numbness before retreatment that remained unchanged during follow-up. All other patients retained intact trigeminal nerve function after GK retreatments. In the literature, the preservation rate of the fifth cranial nerve function ranges from 82% to 100%.^[3,7,9,18]

Adverse radiation effects

None of our patients showed imaging evidence of adverse radiation effects (ARE) after retreatment. Dewan and Norén reported slight peduncular edema in 2 patients after a second GK treatment for VS.^[3] Kano *et al.* described a patient with imaging evidence of ARE without symptoms.^[7] New generations of GK devices provide a higher conformity of GK dosimetric planning that could reduce the incidence of ARE after retreatment of VS.

CONCLUSIONS

When VS regrows after a prior GK procedure and transient volume expansion following irradiation is excluded, GK surgery can be proposed as an alternative to microsurgery when the tumor volume remains within the usual radiosurgical range. Although functional hearing could not be preserved after GK retreatment, none of our patients developed facial or trigeminal nerves dysfunction after a second or third irradiation. This retreatment can serve as an alternative therapy to microsurgical resection in order to improve the preservation of cranial nerve function.

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Conflicts of interest

There are no conflicts of interest.

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