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Gamma Knife Radiation Therapy for Intralabyrinthine Schwannomas

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Abstract

Background: Intralabyrinthine schwannoma are rare benign tumors exclusively managed to date with observation or surgical removal. We analyze results of radiosurgical treatment of these lesions.

Methods: Retrospective analysis of medical data of 454 patients with vestibular schwannomas treated by Gamma Knife in our center was performed. We identify 12 patients treated for a schwannoma located partially or totally into the cochleo-vestibular structures. Ten patients with a clinical and radiological follow-up of more than 1 year were selected for further analysis.

Results: Patients had hearing worsening at different stages, sometimes associated with tinnitus, imbalance or vertigo. The median duration of symptoms before treatment was 3.3 years. Anatomical location of the ILS was intravestibular, intracochlear, intravestibulocochlear, transmacular or transmodiolar (2 patients for each location). We cover 100% of the tumor volume in all patients with a mean margin dose of 11.7 Gy (range 11-12 Gy). The mean follow-up duration was 2.8 years (range 1.5-6.5 years). For 5 patients with functional hearing before treatment, 2 patients had unchanged audiological status at last follow-up, 1 patient had moderate hearing worsening, and 2 patients became cophotic (functional hearing preservation rate of 40%). Facial palsy, even partial and transient, did not occur. No patient experienced permanent worsening of tinnitus, imbalance or vertigo after irradiation.

Conclusions: Gamma Knife radiation therapy seems to be a safe and effective treatment alternative to surgery for patients with intralabyrinthine schwannomas. Radiosurgery can be performed in this indication without significant morbidity with the precision of current robotized Gamma Knife.

Keywords: Intralabyrinthine Schwannomas; Radiation Therapy; Gamma Knife; Radiosurgery; Cochlea; Vestibule; Treatment; Classification; outcome

Introduction

Schwannomas of the vestibular or cochlear nerves are benign tumors that develop from Schwann cells that form the myeline sheaths of nerves. Since Schwann cells unsheathe the nerves from the point at which they penetrate the pia mater to their terminations, schwannomas may originate anywhere along the course of the cochleo-vestibular nerves peripheral to the glial-Schwann sheath junction [1]. The great majority of schwannomas arises in the vestibular division of the VIIIth cranial nerve, inside the internal auditory canal (IAC), and may extend to the cerebellopontine angle. However, schwannomas may also arise from the very distal branches of the cochlear, superior vestibular or inferior vestibular nerves at the level of the sensory end organs [2,3]. These schwannomas arising initially from cochleo-vestibular structures have been called intralabyrinthine schwannomas (ILS) [3] in medical reports. Since the first publication on an autopsy case by Mayer in 1917 [4], less than 300 cases have been reported in the medical literature [3,5-11] ; most of the cases have been found at autopsy or during surgery for intractable vertigo [1,12]. In the last decade, with optimization of MR techniques, the number of reported ILS has gradually increased [3,12].

The common management of ILS includes observation only or different surgical techniques for tumor removal [5,7]. In the present study we evaluate the use of an alternative therapeutic option for the treatment of ILS, Gamma Knife radiosurgery (GKR), which is often used for vestibular schwannomas of the IAC and cerebellopontine angle [13].

Materials and Methods

Patients

In order to identify patients with ILS, we reviewed retrospectively all the radiosurgical cases of our Gamma Knife Center from January 2005 to January 2014. For all these patients, we analyzed the exact location and extension of the tumor by the projection of the contour of the schwannoma performed during treatment planning on the different stereotactic images acquired during the radiosurgical procedure. This investigation allowed us to identify 12 patients with ILS treated by GKR in our center over a 9-year period. During this time interval, we have performed 2502 GKR procedures, including 454 treatments for vestibular schwannomas. So, the incidence of treatment of ILS represents 0.48% of all our indications and 2.6% of GKR performed for vestibular schwannomas. From the 12 patients with ILS treated in our centre, 10 patients with a clinical and radiological follow-up of more than 1 year were selected for further analysis.

All patients included in this study have been referred in our Gamma Knife Center by ENT physicians. The age of our patients ranged from 23 years to 57 years, with a median age of 43 years. There were 5 males and 5 females. The ILS involved the left inner ear in 6 cases and the right ear in 4 cases. The symptoms appeared in our patients from 6 months to 7 years before treatment (median duration of 3.3 years). The main symptom encountered was hearing worsening, which was present in all our patients. For hearing assessment of patients before treatment and during follow-up evaluations, we used the Gardner-Robertson classification [14], as recommended by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS). The preoperative audiological evaluation showed partial hearing loss with maintenance of functional hearing in 5 patients (Gardner-Robertson [14] Classes 1 or 2) and total hearing loss in 5 patients (Gardner-Robertson Class 5). Two patients had tinnitus associated with hearing worsening. Imbalance was present for 4 patients, and vertigo in 1 patient. No patient suffered intractable bothersome vertigo.

Location of ILS

The precise location of ILS was assessed by the use of 3 different imaging performed during the stereotactic GKR procedure: a high-resolution 3D T2-weighted MRI, a high-resolution 3D T1-weighted gadolinium-enhanced MRI, and a high-resolution 3D bone CT-scan acquisition (Figure 1, upper panel). After initial acquisition in stereotactic conditions, we fuse these imaging on the software LGP 9.0 (Elekta Instruments, Stockholm, Sweden). We perform a fusion of T1-MRI with bone CT and T2-MRI with bone CT (Figure 1, lower panel). On these 5 images we can accurately identify the different structures of the inner ear, IAC and middle ear. Extension of the schwannoma into some of these structures can be defined accurately.

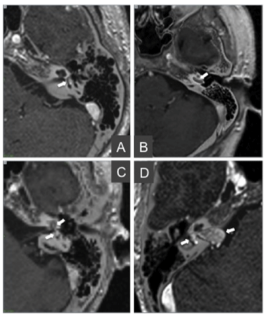

Figure 1: Top: Stereotactic imaging acquisition during GKR procedure: high-resolution 3D T1-weighted gadolinium-enhanced MRI (left), high-resolution 3D T2-weighted MRI (middle), and high-resolution 3D bone CT-scan acquisition (right). Bottom: Image fusions used for dosimetric planning: fusion of MRI-T1gadolinium with bone CT (left), and fusion of MRI-T2 with bone CT (right). The white arrow shows the ILS.

Six patients had schwannomas located only in inner ear structures (Table 1): 2 patients had ILS located into the vestibule, 2 patients had an intracochlear schwannoma, and 2 patients had ILS into both vestibular and cochlear areas. Two patients had an ILS placed within the vestibule with extension to the fundus of the IAC (transmacular), and 2 patients had an ILS located within the cochlea with extension to the fundus of the IAC (transmodiolar). Some examples of different locations of ILS are shown in Figure 2.

Preoperative Characteristics		Value
No of patients		10
Age	median	43 y
	range	23 - 57 y
Sex	male	5
	female	5
Side	left	6
	right	4
Symptoms	duration: median	3.3 y
	duration: range	0.5 - 7 y
	hearing loss - partial (G-R 1-2)	5
	hearing loss - partial (G-R 3-4)	0
	hearing loss - total (G-R 5)	5
	tinnitus	2
	imbalance	4
	vertigo	1
Class / location	Intravestibular (IVE)	2
	Intracochlear (ICO)	2
	Intravestibulocochlear (IVC)	2
	Transmacular (TMA)	2
	Transmodiolar (TMO)	2
Indication for Tt	symptoms worsening	8
	tumor progression	4
Reason for GKR	hearing status	5
	risks of surgery	7

Table 1: Demographic and clinical data of our population. Legend: G-R = Gardner-Robertson classification; Tt = treatment; GKR = Gamma Knife Radiosurgery.

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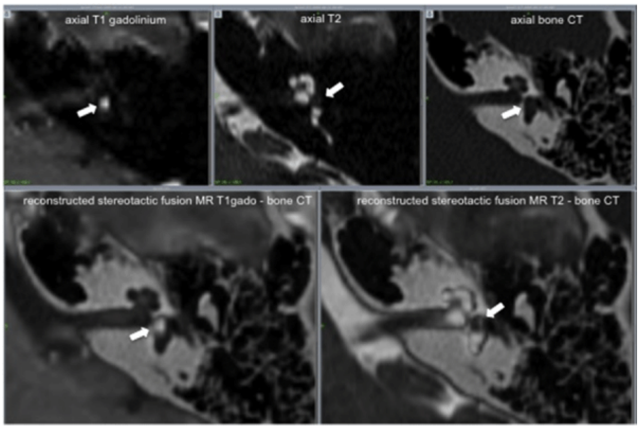

Figure 2: Examples of 4 different locations of ILS: A: class Ia (intravestibular); B: class Ib (intracochlear); C: class Ic (intravestibulocochlear); D: class IIa (transmacular).

Indication for GKR therapy

All patients were initially managed with a conservative "watch-and-scan" approach without treatment. Indication for treatment was related to worsening of symptoms (7 patients) or increase of tumor size on MRI (3 patients). The symptoms that deteriorated were: hearing impairment for 4 patients, imbalance for 2 patients, and tinnitus for 1 patient. For 3 patients, the increase in tumor size was as follows: increase of 3 mm over a 1-year period for 1 patient, increase of 1 mm over a 1-year period for 1 patient, and increase of 1 mm over a 2-years period for 1 patient (mean increase: 1.5 mm/y).

A discussion related to the benefits and risks of microsurgery and GKR have been achieved specifically for each patient in relation with his/her particular medical situation. GKR therapy was preferred to conventional surgery on the basis of the patients hearing status (functional hearing still present) for 5 patients and rejection of the risks related to microsurgery for 5 patients.

Radiosurgical procedure

Three patients underwent a radiosurgical procedure with Leksell Gamma Knife 4C and 7 patients with Leksell Gamma Knife Perfexion. All patients have been treated in a single session of irradiation. Patients were admitted the day before treatment. The next morning, a Leksell G stereotactic frame (Elekta Instruments, Stockholm, Sweden) was attached to the patient's head under local anesthesia with mild intravenous sedation. For all patients, we performed stereotactic high-resolution T1-weighted MRI 3D volume acquisition with Gadolinium-contrast enhancement, stereotactic high-resolution T2-weighted MRI 3D volume acquisition, and stereotactic high-resolution axial bone CT densitometric imaging acquisition. The treatment planning was made on LGP 9.0 (Elekta Instruments, Stockholm, Sweden). We created image fusions of MR-T1gadolinium with CT-imaging and MR-T2 with CT-imaging with the planning software, as shown in Figure 1. The tumour was contoured on axial MR-sequences on the basis of information provided by the different imaging sequences. The conformational dosimetry included coverage of 100% of the tumor volume within the prescription isodose and the sharpest dose fall-off on functional structures around the target (Figure 3a-c).

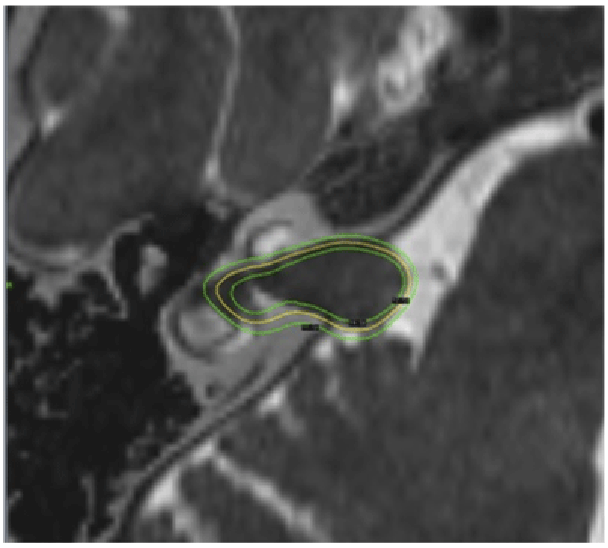

Figure 3: Examples of GKR dosimetric plannings for ILS. 3a. Dosimetric planning of ILS class Ia. Yellow line=1-Gy isodose; internal green line=14-Gy isodose; external green line=8-Gy isodose.

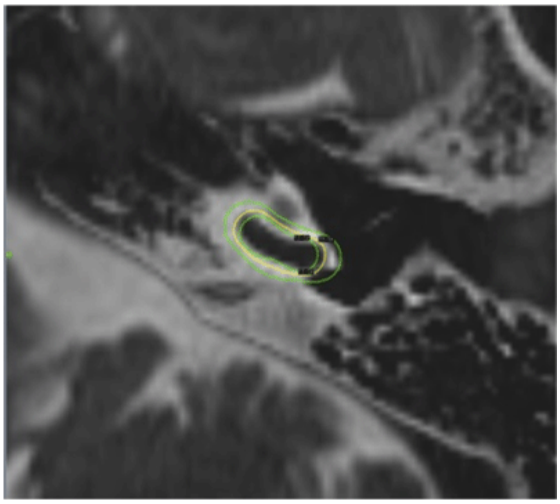

Figure 3b: Dosimetric planning of ILS class Ib. Yellow line=12-Gy isodose; internal green line=13-Gy isodose; external green line=10-Gy isodose.

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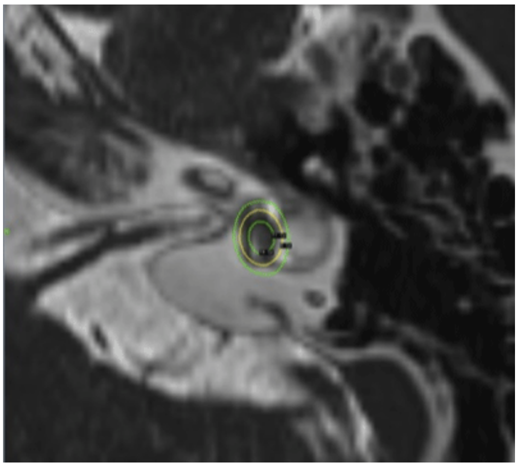

Figure 3c: Dosimetric planning of ILS class IIa. Yellow line=12-Gy isodose; internal green line=14-Gy isodose; external green line=10-Gy isodose.

The patient was placed in prone position on the couch of the Gamma Knife device and the head frame was secured on the robotized positioning system. The treatment planning was applied with Gamma Knife C ou Perfexion, which provides a sub-millimetric accuracy of targeting [13]. The stereotactic frame was removed at the end of treatment. The patients were discharged from the hospital the same day or the next morning.

Results

The main dosimetric parameters of the radiosurgical plannings are presented in Table 2. The tumor volumes of ILS located exclusively in inner ear structures are very low, ranging from 6.4 to 23.3 mm3. The target volume of patient with ILS extending into the IAC ranged from 9 to 399.5 mm3. We used 1 to 13 isocenters of 4-mm diameter, and we blocked some of the beams to improve conformity for 7 patients. The mean margin dose was 11.7 Gy (range 11-12 Gy) prescribed at the 50%- to 85%-isodose (median: 70%-isodose). The mean maximal dose ranged from 13.8 to 24 Gy (mean: 17.5 Gy). The Paddick Conformity Index [15] ranged from 0.13 to 0.84 and the integrated dose ranged from 0.1 to 6.5 mJ.

Patient No.	Location	Tumor max length (mm)	volume (mm3)	Dosimetry nb isocenters	BCB	margin dose (Gy)	isodose %	max. dose (Gy)	coverage %	C.I.	Int. dose (mJ)
1	IVC	2.8	9.5	1 x 4 mm	no	12	80%	15	100%	0.29	0.1
2	IVE	3.6	9.3	1 x 4 mm	no	12	85%	14.1	100%	0.38	0.1
3	IVC	3.8	13	1 x 4 mm	no	12	80%	15	100%	0.39	0.2
4	IVE	3.7	23.3	1 x 4 mm	yes	12	70%	16	100%	0.62	0.3
5	TMA	16.6	399	13 x 4 mm	yes	12	50%	24	100%	0.78	6.5
6	TMO	4.9	9	1 x 4 mm	yes	12	65%	18.5	100%	0.15	0.1
7	ICO	5.1	17.5	2 x 4 mm	yes	11	60%	18.3	100%	0.2	0.2
8	TMO	4.1	9.1	1 x 4 mm	yes	12	65%	18.5	100%	0.13	0.1
9	ICO	4.5	6.4	3 x 4 mm	yes	11	80%	13.8	100%	0.19	0.1
10	TMA	5.1	39.5	2 x 4 mm	yes	11	70%	22	100%	0.84	0.5

Table 2: Dosimetric data. Legend: BCB=beam channel blocking; C.I.=Paddick Conformity Index; Int. dose=integrated dose; IVE=intravestibular; ICO=intracochlear; IVC=intravestibulocochlear; TMA=transmacular; TMO=transmodiolar.

Clinico-radiological follow-up evaluations were available for 10 patients. The mean follow-up duration was 2.8 years and ranged from 1.5 to 6.5 years (Table 3). Since no patient experienced tumor growth after irradiation, the tumor control rate was 100%. Two patients experienced a significant reduction of tumor volume after treatment. Five of the 10 patients were cophotic before treatment. For 5 patients with useful hearing before GKR, maintenance of useful hearing was achieved for 2 patients, moderate audiological worsening occurred for 1 patient, and 2 patients became cophotic during the follow-up after irradiation. Of the 6 patients with ILS involving the cochlea, 4 were cophotic before treatment; both patients without preoperative cophosis had hearing worsening after irradiation. So, patients with ILS involving the cochlea are at higher risk of hearing loss after radiosurgical treatment. Other symptoms (tinnitus, imbalance, vertigo) were unchanged for half the patients and improved significantly after treatment for the other half.

Follow-up			
No of patients			10
Duration	mean		2.8 y
	range		1.5 - 6.5 y
Tumor volume	increased		0

	stable		8
	decreased		2
Hearing outcome	cophosis before treatment		5
	worsened	(GR 2→3)	1
		(GR 2→5)	2

Table 3: Outcome data. Legend: GR=Gardner-Robertson classification.

Discussion

Only a limited number of scientific articles have reported patients with ILS; these papers were mainly case reports or small series the optimal management of these patients remains controversial and is always discussed between observation and surgical removal in the medical literature. To the best of our knowledge, our series represents the first publication on ILS treated radiosurgically.

Intralabyrinthine schwannomas

The incidence of vestibular schwannomas has gradually increased in the last decades. Several factors are believed to be the cause of this increase. The main reason could be the improving diagnostic equipment and better access to MRI. The heightened symptom awareness among the general population, the healthier and longer lifetime in developed countries, and the better and more widespread audiologic testing equipment could also have contributed to the growing incidence of vestibular schwannomas.

In a recent study on the evolution of incidence of vestibular schwannomas in Denmark, Stangerup et al. have found an increase from 3.1 per million per year in 1976 to a stable rate of about 19 tumors per million per year [16]. The authors found that the sex ratio and age have remained grossly unchanged over the years but that hearing has improved and tumor size has decreased considerably. Particularly, the proportion of intrameatal schwannomas diagnosed has greatly increased. In the same way, ILS was not found by imaging since the use of very sensitive MR techniques. In 2008, Tieleman et al. have reported the largest series of ILS to date [3]. They found 52 ILS over a 16.5-year period in 2 referral centers specialized in temporal bone imaging, representing up to 10% of all VIIIth nerve schwannoma diagnosed. In our center, about 2.6% of all vestibular schwannomas treated in the last 9 years have concerned ILS.

The most common symptom experienced by patients with ILS is unilateral hypoacousia, mostly progressive [7,17]. In our series, all patients suffered from hearing worsening at different stages, from mild hypoacousia with functional hearing maintained to complete hearing loss. In discordance with series of patients with ILS treated surgically, some patients of our series were treated when hearing was still useful. Tinnitus, imbalance or vertigo is also common symtoms in patients with ILS [5, 7-12]. No patient of our series suffered intractable bothersome balance disorders since this trouble is considered in our center as indication for resective surgery and a contra-indication for GKR.

Management of ILS

The optimal management of ILS remains to be defined [5]. Some authors advocate initial observation for all cases [7,8,17], though others recommend surgical removal for most patients [5,12]. Many authors consider that the optimal therapeutic approach must be defined individually for each patient since several factors could be involved in the decision, such as patient's age, hearing status, and presence of bothersome intractable symptoms such as vertigo or tinnitus [3,7]. The hearing level is often considered as a main determining factor, since microsurgery will consistently bring to complete hearing loss [17,18]. Therefore, a majority of authors recommend surgery only for patients with cophosis or intractable bothersome symptoms (vertigo/tinnitus) and observation for patients with serviceable hearing [8,17-19].

In their study Tieleman et al [3] have analyzed the prevalence of tumor growth in patients with ILS. From the 27 patients with a follow-up imaging available, they found tumor growth in 59% of cases. This has been confirmed by the recent study of Van Abel et al [10]. Other authors have also reported proven tumor growth of ILS [12,17,19]. Accordingly, management of ILS with observation without treatment will get at the long-term many patients to worsening of symptoms, especially hearing loss, because of tumor growth. The main reason to manage patients conservatively is that some tumors will remain stable with time. For patients who experienced tumor growth or worsened symptoms with time, observation without treatment is often maintained until patients became cophotic, since surgery is associated with significant risk of morbidity with total hearing loss in all patients, worsening of preoperative symptoms, and facial palsy in some cases [7,19]. A new therapy for ILS that will prevent tumor growth and that will not systematically produce hearing loss or other complications will be welcome.

Radiosurgery has become the most common therapeutic option for patients with vestibular schwannomas. This treatment has already proved its efficiency and safety in this indication [13]. The long-term tumor control rate is superior to 90% in the current series. The morbidity has been reduced with the use of low radiation dose: a margin prescription dose ≤13 Gy is associated with an incidence of hearing worsening after treatment of less than 30% in most series [13,20]. Facial nerve dysfunction after radiosurgery is very low and essentially partial and transient with an optimal GKR procedure [13]. Corticoids may be used in selected cases to reduce the adverse clinical effects of transient edema that may occur after irradiation. The main benefits of GKR come from the absence of microsurgical dissection of sensitive structures such as the cochleovestibular and facial nerves. A general anesthesia is also not necessary. This provides a significant reduction of morbidity compared with conventional surgery.

The present study reports the first series of patients with ILS treated by radiation therapy. ILS are benign schwannomas histologically similar to vestibular schwannomas located in the IAC and/or pontocerebellar angle [1,12]. ILS has some specific characteristics that may influence the results of this therapy. ILS is located in structures sensitive to radiation [21]. ILS is often of low volume and could be irradiated radiosurgically with a very sharp dose fall-off outside the target [22]. The current procedure of GKR with devices equipped of fully robotized patient positioning system allows treatments with very accurate precision of targeting, often significantly less than 0.5 mm [23]. We experienced 5 patients with ILS and useful hearing treated by GKR. Their audiological status remained unchanged after treatment for 2 patients and only partially worsened for 1 patient; only 40% of patients became cophotic after GKR. We have observed that early radiosurgical irradiation of vestibular schwannomas located in the IAC and/or pontocerebellar angle when hearing is still highly functional is associated with a higher rate of hearing preservation [20]. More experience is warranted to define the hearing outcome after GKR for ILS in non-cophotic patients.

Few authors have included stereotactic radiosurgery in their discussion on current therapeutic management of ILS [7,8,17]. To our knowledge, there is no article in the medical literature reporting a radiosurgical treatment of ILS. Some authors state that radiosurgery is not a valuable option for ILS [8,17]. They assume that radiosurgery is at risk of facial palsy and would systematically cause hearing loss; however, this statement is purely speculative and not based on objective results. In the current worldwide experience of contemporary GKR for vestibular schwannomas located in the IAC and/or cerebellopontine angle, permanent facial palsy did not occur when optimized dosimetry and low radiation doses (usually below 13 Gy) are used [13,24]. For ILS radiosurgery, the radiation target is much more distant from the facial nerve than GKR for vestibular schwannomas located into the IAC, which represents a significant part of the schwannomas currently treated radiosurgically [16,25,26]. Our experience also states that GKR treatment for ILS has not induced facial palsy and is able to maintain useful hearing in some cases.

As others [7], we consider that radiosurgery is not the optimal therapy for patients with intractable bothersome vestibular symptoms. We disagree with Kennedy et al. [7] who state that radiosurgery must be reserved only for old patients with proven tumor growth. Indeed, the high efficiency and low morbidity that seem associated with GKR for ILS could probably make this treatment a valuable therapeutic option even for young patients. GKR seems to be the only therapeutic option to date that allows controlling tumor progression and maintaining useful hearing for the long-term.

Conclusions

ILS is diagnosed more frequently in the recent years in patients with hypoacousia or vestibular symptoms, mainly because of the development and widespread use of high-resolution MRI. GKR represents a valuable therapeutic option for these tumors, with a high rate of tumor control and a low morbidity. Based on our preliminary experience, we recommend that patients are initially managed by observation and patients with intractable bothersome vestibular symptoms are treated by surgery. Patients with tumor growth or worsening of symptoms (including hearing) could be treated by GKR, especially patients with functional hearing still present.

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