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Gamma Knife surgery in vestibular schwannomas: impact on the anterior and posterior labyrinth

Clinical article

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Object. During the past decades, in small-to-medium size vestibular schwannomas, Gamma Knife surgery (GKS) has become a reliable therapeutic option because of either excellent local tumor control or minimal morbidity, with cranial neuropathy becoming increasingly rare. Although still insufficiently analyzed in larger cohorts of patients with long-term follow-ups, adequate chances of hearing preservation and vestibular sparing seem clinically guaranteed. However, deeper investigations are needed in this regard, expanding the number of cases and the follow-up period.

Methods. A small group of patients with vestibular schwannomas (74 patients, including 41 men and 33 women) treated between 2003 and 2009 using GKS at the authors' institution were analyzed—both before and after GKS—with computerized static stabilometry and electronystagmography for balance disorders, vertigo, and ataxia on 1 side and pure tone average, vocal speech discrimination score, auditory brainstem response, and so forth for hearing impairment and tinnitus on the other side. Eligibility criteria for this prospective study included previously untreated unilateral lesions and a Gardner-Robertson hearing class of I–III. Dosimetry plans had been programmed at the lower effective dosages for these tumors (median surface dose 12.4 Gy, range 10–13 Gy), carefully avoiding even minimal toxic dosages on the most vulnerable targets: the cochlea (never > 6 Gy) and the vestibular canals (< 7.5 Gy).

Results. To date, tumor growth control rates remain satisfactory; at a mean follow-up of 50 months, the rate was 96%. The overall level of hearing preservation was 72%, with 81% having Gardner-Robertson Class I hearing. Tinnitus decreased, from 52% to 28% of patients ($p < 0.01$). Significant improvements were also observed in vestibular symptoms, with computerized static stabilometry abnormalities decreasing from 62% to 32% ($p < 0.001$) and electronystagmography abnormalities reducing from 48% to 14% ($p < 0.001$).

Conclusions. Using appropriate radiodosimetry planning, GKS seems to guarantee not only adequate tumor growth control rates, but also better levels of hearing preservation, with a documented, long-lasting improvement in vestibular functions. *(DOI: 10.3171/2010.8.GKS101089)*

Key Words • radiosurgery • Gamma Knife • vestibular schwannoma • labyrinth

It is generally accepted that the majority (more than 90%) of "acoustic neuromas" are indeed VSs–mostly from the inferior branch–originating in the "fibrous cone" where the oligodendroglial sheathing is substituted by Schwann cell coverage.[6,14,23] A strict minority (3–10%) seem to belong to the cochlear nerve, the Scarpa ganglion, the vestibule, and the fundus.[5,8,25] This probably explains the relevance of balance impairment and hearing disturbances in patients with these lesions as well as the predominance of deficits following the surgical removal of such tumors. In small-to-medium VSs, GKS currently represents a major therapeutic option, basically because of the highly conformal and selective dose planning, excellent rate of tumor control, and minimal morbidity in terms of cranial neuropathy.[2,9,11,15–17,20,21,24,26] The increasing role of such a peculiar approach has been further confirmed by a recent Acoustic Neuroma Association survey of US patients with acoustic neuromas (Table 1).[1]

In these patients, once again, GKS treatments have been followed by high levels of TGC, maintaining an undoubtedly low overall incidence of side effects (Table 2) basically confined to the cochlear and vestibular components, with extremely rare involvement of the facial nerve.[3,11,16,17,20,26] These results were similar to our own

Abbreviations used in this paper: CSS = computerized static stabilometry; ENG = electronystagmography; GKS = Gamma Knife surgery; G-R = Gardner-Robertson; MFU = mean follow-up; PTA = pure tone audiometry; SDS = speech discrimination score; TGC = tumor growth control; VS = vestibular schwannoma.

TABLE 1: Acoustic Neuroma Association US 2007–2008 survey of over 2000 evaluable forms*

Parameter	% Patients				
	Microsurgical Treatment		Stereotactic Radiosurgery Treatment		Wait & Watch
survery year					
1983	100		0		0
1998	85		5		10
2008	61		20		19
sequelae	Preop†	Postop†	Preop	Postop	
hearing loss					
G-R Class I–III	67	16	56	23	
G-R Class IV–V	33	84	44	77	
balance deficit	34	61	11	25	
facial deficit					
H-B Grade I–II	84	43	96	79	
H-B Grade V–VI	11	16	0	2	

* H-B = House-Brackmann.
† Nontranslabyrinthine approach.

experience with GKS for VS: from the very beginning, a negligible percentage (2%–3%) of facial neuropathy was associated with a 36% rate of acoustic, and a 28% rate of balance, deterioration.[9]

Consequently, some of the newer goals of a refined technique are strictly related to the cochlear and vestibular structures of the involved side, aiming to improve functional results for both. Briefly, accurate dose planning may enhance hearing preservation, adequately sparing the cochlear region, the most vulnerable of the acoustic "topography." The process must be monitored with appropriate and repeated audiometric staging. Vestibular protection can be achieved first with accurate monitoring of the related functions by using ENG and CSS,[28,29] followed by carefully reduced radiation exposure of the semicircular canals. Such a strategy and the relevant follow-up analyses must separately consider all the various specific segments: receptor, nerve fiber, nuclear, and ganglionic regions. This study was planned to evaluate the impact of this approach on both the anterior and the posterior labyrinth.

TABLE 2: Literature summary of studies on GKS for VS: results in terms of TGC

Authors & Year	No. of Patients	MFU (mos)	TGC (%)
Norèn, 1998	250	36	95
Kondziolka et al., 2000	162	60	98
Unger et al., 2002	100	76	96
Gerosa et al., 2002	112	49	93
Iwai et al., 2003	51	60	86
Litvack et al., 2003	121	32	96.7
Régis et al., 2004	1000	84	97
Beegle et al., 2007	390	60	91
Arthurs et al., 2010	70	26	94
present study	74	50	96

Methods

Between February 1993 and April 2010, 602 patients harboring symptomatic VSs were treated with GKS (Model C and Perfexion, Elekta AB) at our institution. A smaller group of 74 patients (those since 2003) consisting of 41 men and 33 women, with a mean age of 59 years (range 24–77 years), was considered for the purpose of this research.

Eligibility criteria included the following: unilateral VS, no previous surgical or radiation treatment, no concomitant hydrocephalus, no systemic neurological disorders, and, finally, a G-R hearing class of I–III, that is, beyond the traditional threshold of "serviceable hearing" (G-R Class I–II). This criterion was decided to explore minimal variations in residual cochlear function or to analyze the potential role of acoustic devices under these conditions.[3,4,7,10,19,22,24]

TABLE 3: Treatment planning parameters in 74 patients*

Parameter	Value
ATV in cm^3 (range)	2.7 (0.06–10.4)
mean peripheral isodose in % (range)	51.7 (50–60)
median surface dose in Gy (range)	12.4 (10–13)
mean no. of isocenters	14.6 (2–23)
mean conformity index (range)	1.28 (1–2.35)
max receptor exposure (Gy)†	
cochlea	5
vestibular channel	7.2

* ATV = average tumor volume.
† Max receptor exposure is the maximum dose reaching 3 mm^3 of the receptor volume.

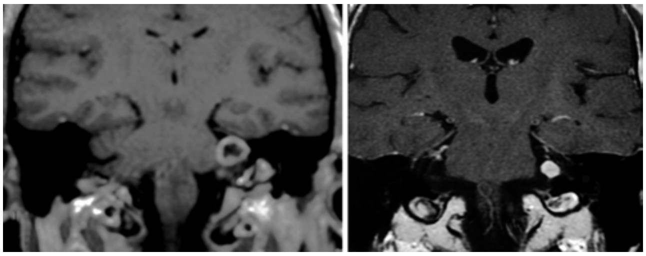

Fig. 1. Coronal MR images with contrast medium showing a VS 7 **(left)** and 41 **(right)** months after GKS, with evident tumor shrinkage.

A clinicoradiological diagnosis was routinely based on CT (including bone algorithm) and accurately selected MR imaging sequences (volume acquisition, constructive interference for steady state [CISS], fat suppression, and so forth). Patient quality of life was assessed according to the Karnofsky Performance Scale, starting with an average of 73 before radiosurgery.

Cochlear and vestibular functions were assessed on 1 side before and after GKS by using pure tone audiometry, auditory brainstem response, and vocal SDS; on the other side, by testing reflectivity according to the Hallpike-Fitzgerald method, "corticospinal balance" using CSS, and vertigo using ENG.

On admission, 50% of the patients reported slowly progressive hypacusia, 4% reported a sudden deficit, and 6% reported a variable alternating trouble. Sixteen (21.6%) of 74 patients had G-R Class I hearing; 20 (27%) had G-R Class II; and 38 (51.4%) had G-R Class III.

Tinnitus was present in 56.7% of the cases.

Regarding vestibular symptoms, balance disorders (mainly ataxia) were present in 63.5% and vertigo in 46% of patients.

Dose Planning

Dose planning was done in consideration of the tumor size—although as low a dose as possible was selected—tumor location, and projected radiobiological risk to adjacent brainstem and cranial nerve. The mean peripheral dose was 12.4 Gy (range 10–13 Gy), and the mean number of isocenters was 14.6 (range 2–23 isocenters). The main parameters are summarized in Table 3.

Patient Follow-Up

Patients were regularly monitored at 6 and 12 months

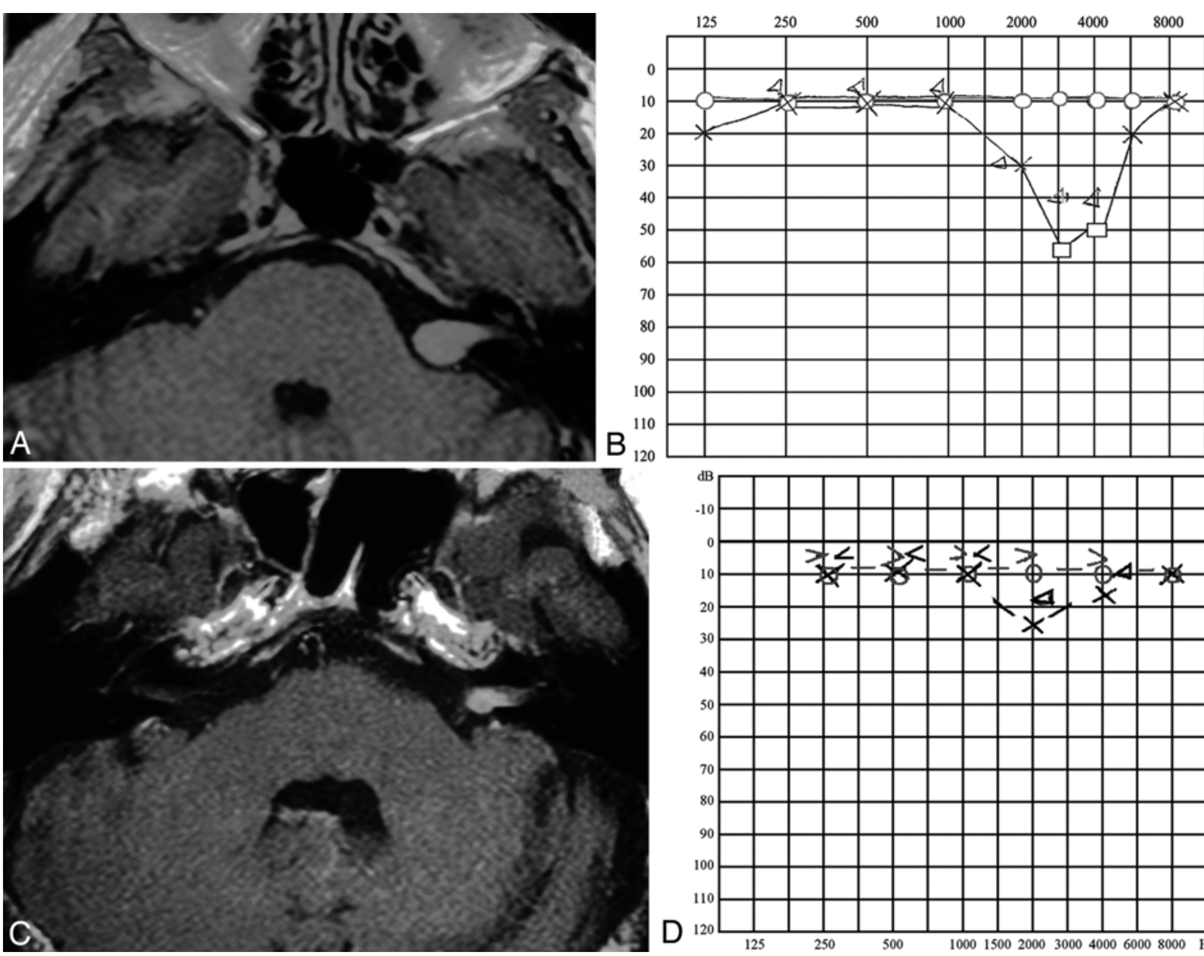

Fig. 2. Magnetic resonance images with contrast medium **(A and C)** and graphs **(B and D)** featuring fluctuating audiometric recovery. Left VS 6 **(A and B)** and 18 months **(C and D)** after GKS. The progressive tumor shrinkage is associated with fluctuating audiometric recovery.

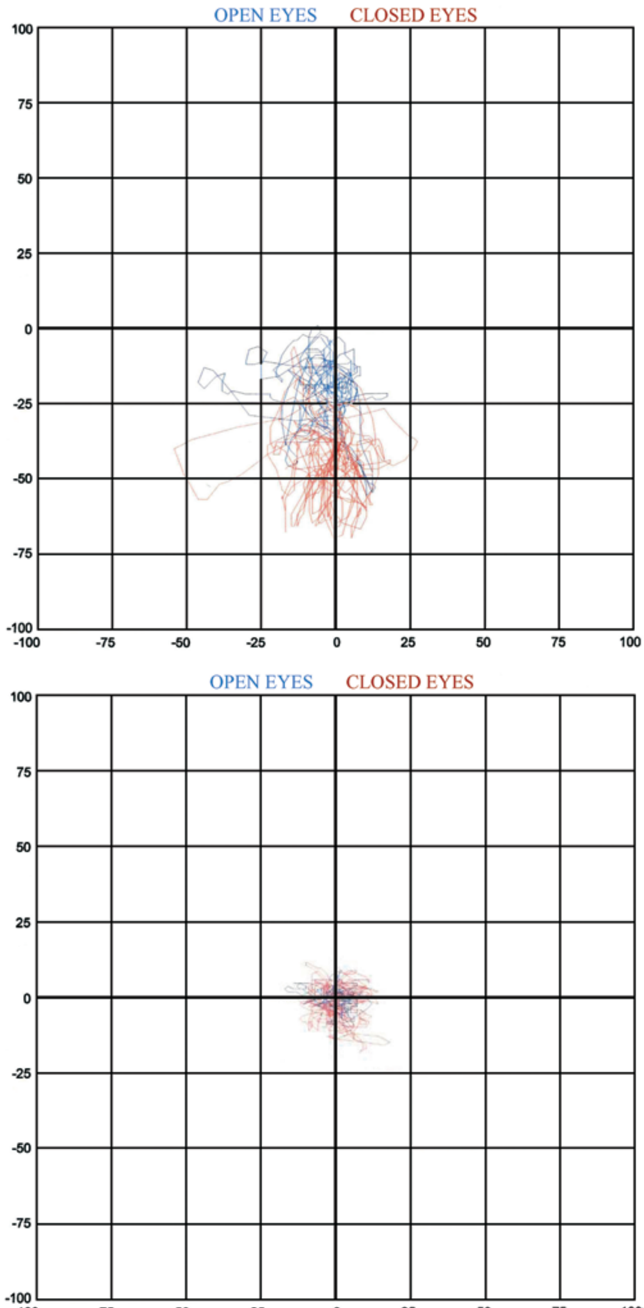

Fig. 3. Computerized static stabilometry. Basic statokinesigraph evaluates control systems of fine postural adaptation with open and closed eyes when moving right to left (x axis) or posterior to anterior (y axis). Stabilograph measures the mean position of the gravity center of the body. **Upper:** Postural control before GKS. Statokinesigraph showing evidence of back leaning. **Lower:** Post-GKS 59-month follow-up, normalized (statokinesigraph isocentric).

after GKS and subsequently every 12–18 months, repeating the same MR imaging sequences and otologic and neurootologic tests, that is, pure tone audiometry, auditory brainstem response, vocal SDS, CSS, and ENG with bithermal caloric tests. Data collection in this study was performed at an MFU of 50 months (12–74 months).

Statistical Analysis

Statistical analysis was performed using the general Student t-test. On the basis of criteria usually accepted internationally, values of $p \leq 0.05$ were considered statistically significant.

Results

Despite the slightly reduced targeting dose, TGC was achieved in 96% (71 of 74) of these patients in terms of either growth arrest with no significant reduction in tumor volume or evident tumor shrinkage (> 20% decrease in size; Fig. 1). In 3 (4%) of 74 cases, a mild increase in tumor volume was observed and is now being monitored for possible surgery. In all 3 of these patients–considering the time interval, the MR image, and so forth—it might still be a transient phenomenon.[2–4,13,19,21,22] Nonetheless, this kind of neoplastic "progression" was invariably associated with audiometric worsening.

In patients with G-R Class I hearing, the preservation rate reached 81.2% (13 of 16 patients), 60% (12 of 20 patients) in those with G-R Class II, and 79% (30 of 38 patients) in those with G-R Class III. The SDS did not change during the 1st year in patients with G-R Class I or III hearing, although the overall rate of hearing preservation was 72% ($p \leq 0.001$) at the final follow-up. No patient has reported anacusia thus far. In addition, a small cohort of patients showed audiometric patterns of "fluctuating Ménière-like hypacusia," that is, an early deficit followed by functional recovery, sometimes in a repeated sequence within a few months. Such an event was eventually correlated with tumor shrinkage (Fig. 2).

Moreover, in the mid- to long-term follow-up, most patients experienced a marked reduction in or disappearance of tinnitus, with a nonnegligible statistical decrease from 52% before GKS to 28% at the follow-up ($p \leq 0.01$).

Significant improvements in vestibular symptoms were observed several years after treatment as well, which may partially explain the increased Karnofsky Performance Scale score (from 73 to 85). The reduced incidence of balance disorders was further confirmed by the significantly lower rates of abnormal CSS on both axes (from 62% to 32%, $p \leq 0.001$; Figs. 3 and 4). Computerized static stabilometry may nicely document the peculiar recovery of balance control in these patients. These pictures regularly paralleled the Freyss-graphed ENG results (from to 48% to 14%, $p \leq 0.001$; Fig. 5).

Finally, no new deficit in the trigeminal or facial pathways was ever observed in this group of patients, and neither were there any other major neurological complications (hydrocephalus, diplopia, and so forth).

Discussion

During the last decades, stereotactic radiosurgery, particularly GKS, has gained an increasing reputation as a solid alternative to microsurgery in VSs of limited size, preferably those with a pons-petrous distance ≤ 20 mm.[2,7,10,11] Since the early positive experiences of Norén in the 1970s,[17] overall results have gradually improved in terms of unprecedented higher precision in target local-

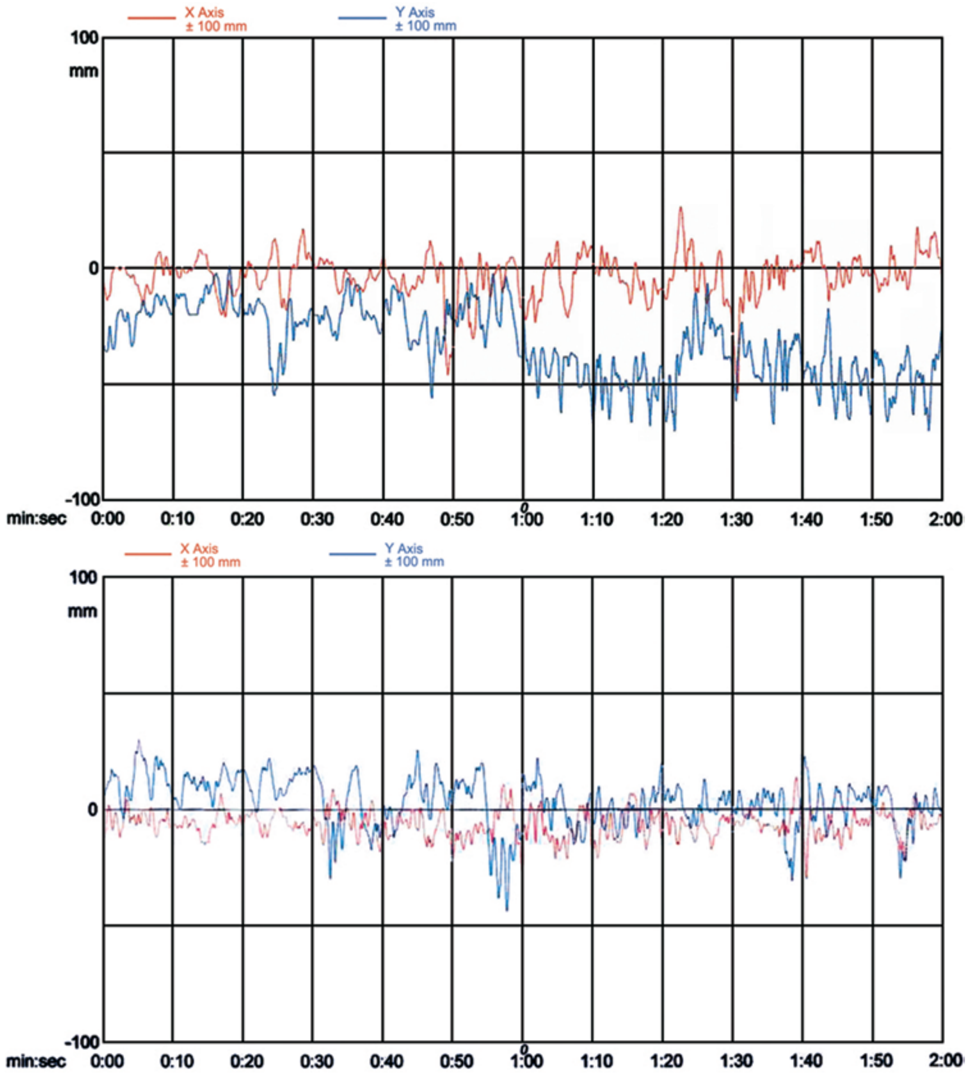

Fig. 4. Same case featured in Fig 3. **Upper:** Stabilogram obtained at GKS. Tilting of the body axis along the x and y coordinates in the time domain. **Lower:** Stabilogram obtained 59 months later (normal).

ization—basically due to advances in CT, MR imaging, and stereoimaging—and in terms of novel algorithms introduced in computerized dose planning and automatic positioning system devices. The technique has reached extremely rewarding conformity and selectivity indexes, thanks also to the use of microshots in highly multifocal treatment plans.[2,3,9,11,19–21]

Furthermore, radiotoxicity thresholds for cranial neuropathy have been extensively analyzed, and their "radiovulnerability grading" covers a wide spectrum of dosages, with pronounced inhomogeneity among the different cranial nerves and the various nerve regions, given that radiation sensitivity may vary quite significantly from the receptor to the ganglion and from the nucleus to the nerve fibers of the same cranial nerve.[3–6,12,13,15,18,21]

These aspects are particularly emphasized in cranial nerves VII and VIII. The most critical segments are probably represented by the geniculate ganglion along the facial pathways, as well as by the cochlear region among the acoustic pathways and structures.[13,21,22,26] For both of these structures, dose-volume analysis is not feasible because of their small sizes.[4] At these levels, the therapeutic dose must be drastically reduced or, if necessary, split for a staged procedure given that the internationally accepted radiotoxic thresholds are approximately 4–5 Gy for the cochlea, 7–8 Gy for the semicircular canals, and 9–10 Gy for the geniculate ganglion.[7,10,16,22,24,26] However, no benefit from fractionation should be expected for VSs with a low alpha/beta ratio.[27]

Dose exposures of the various temporal bone structures during routine GKS for VSs have been carefully investigated,[12] thereby providing a basic "topographic" dosimetry in patients (Table 4). As a consequence, alternative radiosurgical strategies have been proposed: first, to decrease treatment dose levels with the aim of reducing the incidence and relevance of side effects, without eventually altering the excellent TGC rates; and second, to refine and model the matching isodose to obtain the minimal possible exposure of the most susceptible structures, that is, the cochlea and the vestibular canals.

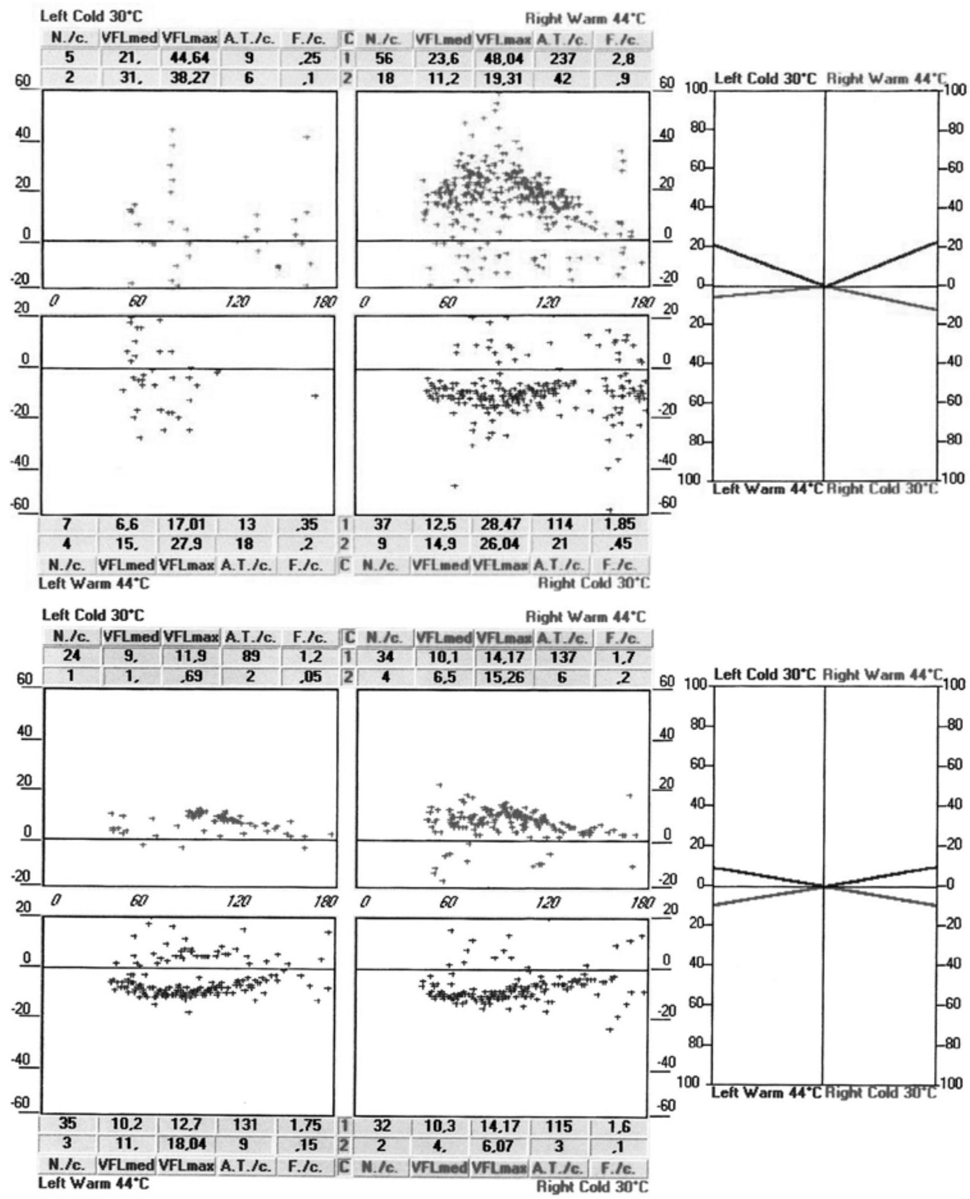

Fig. 5. Freyss graphs before and after GKS. **Upper:** Left VS ENG at the thermic stimulation before GKS. Note the reduction on the left side compared with the other (left vestibular hypofunction). **Lower:** Vestibular schwannoma Freyss graph at the 40-month follow-up showing normalization.

TABLE 4: Dose exposure of normal temporal bone structures during routine GKS in 54 patients*

Region	Dose
intratemporal facial nerve	16% received > surface dose
cochlea (basal turn, nerve modiolus)	11% exposed to > 10 Gy
vestibular labyrinth (ends dilated as ampulla, lat & pst semicircular canals)	7.5% exposed to > 12 Gy

* Median surface dose was 13 Gy. Abbreviation: pst = posterior.

Preliminary reports of adequate series of patients with more than 3 years of MFU seem to confirm that treatment planning based on slightly reduced edge doses (between 11 and 12.5 Gy) does not alter the overall TGC[7,16,20,21,26] and may even spare or possibly enhance cranial nerve VIII function (Table 5).

Our results seem to validate this approach, first of all confirming at lower dosages the maintenance of TGC levels (96% at a 4-year MFU) typical of this technique, with excellent protection of hearing function (72% at a 4-year MFU). Moreover, there is additional evidence of the well-known phenomenon of fluctuating hypacusia, presumably linked to mechanical compression (edema) of the nerve fibers. Indeed, in the natural history of VSs, the majority

TABLE 5: Literature survey of studies featuring a comparison between hearing preservation and the tumor margin dose in patients with normal hearing before radiosurgery

Authors & Year	No. of Patients	No. of Patients w/ G-R Class I	FU (yrs)	Median Surface Dose (Gy)	Useful Hearing (%)
Norén, 1998	254	—	3	13.6	60 (at 2 yrs)
Kondziolka et al., 2000	162	—	5–10	16	47
Prasad et al., 2000	153	96	4.27	13	58
Flickinger et al., 2004	198	—	2.5	13	71
Unger et al., 2002	60	29	1–8	13	55
Régis et al., 2004	1000	175	7	12.74	60 (at 3 yrs)

of patients with these lesions have hearing loss progression of 6–13 dB per year.[15,18,24]

Regarding single-stage radiosurgical treatments, most believe that to spare cochlear function, the tumor edge dose should never exceed the threshold of 13 Gy (Table 5).[4,7,10,13,15,18,22,24,26] According to Régis and colleagues,[21,22] under these conditions, patients with G-R Class I hearing who are treated with GKS have a 78% chance of hearing preservation.

Finally, this study provides additional evidence that lower dosages with extremely fitting isodoses sparing the vestibular labyrinth may not only protect balance and coordination (one-half to one-third of the patients clinically improved) but also provide functional recovery, with normalization of the statokinesigraph and the Freyss profile.[28,29]

Conclusions

Data in this cohort of patients seem to confirm that newer treatment planning strategies may improve radiosurgical results in VSs in terms of hearing preservation and vestibular protection. In short, for the best results, use 1) accurate targeting of the cochlea and the semicircular canals with MR imaging/CT bone algorithm fusion, 2) reduced radiation dosages, and 3) absolute sparing of the receptor sites.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Gerosa. Acquisition of data: Gerosa, Mesiano, Longhi, De Simone, Foroni, Nicolato. Analysis and interpretation of data: all authors. Drafting the article: Gerosa, Mesiano, Nicolato. Critically revising the article: Gerosa, Longhi, De Simone, Foroni, Verlicchi, Zanotti, Nicolato. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Mesiano. Administrative/technical/material support: Verlicchi, Zanotti. Study supervision: Gerosa, Nicolato.

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