Strahlenther Onkol
https://doi.org/10.1007/s00066-018-1361-8

ORIGINAL ARTICLE

Radiosurgery of vestibular schwannoma: prognostic factors for hearing outcome using 3D-constructive interference in steady state (3D-CISS)

Franca Wagner[1] · Matteo Gandalini[1,2] · Arsany Hakim[1] · Ekin Ermis[3] · Dominic Leiser[3] · Martin Zbinden[1] · Lukas Anschuetz[4] · Andreas Raabe[5] · Marco Caversaccio[4] · Roland Wiest[1] · Evelyn Herrmann[3]

Received: 30 June 2018 / Accepted: 17 August 2018

Abstract

Purpose Stereotactic radiosurgery (SRS) is an effective treatment for vestibular schwannoma (VS). Three-dimensional (3D) constructive interference in steady state (CISS) is the preferred magnetic resonance imaging (MRI) sequence for evaluating signal changes in the inner ear endolymph. Previous studies demonstrated a correlation between pretreatment cochlear signal intensity in 3D-CISS and posttherapeutic hearing outcomes. The purpose of our study was to compare 3D-CISS sequences before and after primary SRS of unilateral VSs to evaluate the effect of radiosurgery on the 3D-CISS signal intensities of cochlea and sacculus/utriculus.

Methods We retrospectively reviewed 47 patients with unilateral VS treated with SRS. The neuroradiological MRI datasets were analysed to evaluate the signal intensity of the inner ear structure, tumour size, Koos grade, tumour volume, and infiltration of the cochlear aperture before therapy and at follow-up. The differences in these signal intensities before SRS and at follow-up were correlated with clinical symptoms, cochlear radiation dose, tumour volume and infiltration of the cochlear aperture.

Results No differences were found between signal intensities in cochlea and utriculus/sacculus before and after SRS and no correlation with clinical symptoms, cochlear radiation dose, tumour volume, Koos grade or infiltration of the cochlear aperture (all $p > 0.05$).

Conclusion Our study supports the theory of a complex interaction causing alteration of the endolymph protein concentration and not a direct dependency on the SRS. Use of modern dosing schemes will have a positive impact on clinical outcome with preservation of hearing in patients with VS.

Keywords 3D-CISS · Labyrinth signal loss · Magnetic resonance imaging · Vestibular schwannoma · Radiosurgery

✉ Franca Wagner, MD
franca.wagner@insel.ch

[1] Institute for Diagnostic and Interventional Neuroradiology, University Hospital Bern and Inselspital, Freiburgstraße 4, 3010 Bern, Switzerland

[2] Departments of Radiology, Radiotherapie and Radiology Practice, Konstanz, Germany

[3] Departments of Radiation Oncology, Inselspital, University of Bern, Bern, Switzerland

[4] Departments of Otorhinolaryngology and Head and Neck Surgery, Inselspital, University of Bern, Bern, Switzerland

[5] Departments of Neurosurgery, Inselspital, University of Bern, Bern, Switzerland

Published online: 10 September 2018

Radiochirurgie bei Vestibularisschwannom: Prognostische Faktoren für das Hörvermögen bei Akquisition der 3D-CISS

Zusammenfassung

Ziel Stereotaktische Radiochirurgie („stereotactic radiosurgery", SRS) ist effektiv zur Behandlung des Vestibularisschwannoms (VS). Die 3-D-CISS-Sequenz („constructive interference in steady state") ist die Sequenz der Wahl bei der Magnetresonanztomographie (MRT) zur Auswertung von Signalveränderungen der Endolymphe des Innenohrs. Frühere Studien zeigten eine Korrelation zwischen der Signalintensität der Cochlea in der 3-D-CISS vor Strahlentherapie und dem Hörvermögen nach Bestrahlung. Ziel der vorliegenden Studie war der Vergleich der Signalintensität von Cochlea sowie Sacculus/Utriculus in der 3-D-CISS-Sequenz vor und nach primärer SRS.

Methoden Retrospektiv wurden 47 Patienten mit einseitigem VS und SRS-Therapie untersucht. Eine neuroradiologische Analyse der initialen und Verlaufs-MRT mit 3-D-CISS erfolgte, um die Signalintensität des Innenohrs, Tumorgröße, den Koos-Grad, das Tumorvolumen und die Infiltration der Cochlea-Apertur vor SRS und im Verlauf zu evaluieren. Die Unterschiede der Signalintensität vor SRS und bei der Nachuntersuchung wurden mit den klinischen Symptomen, der applizierten Strahlendosis an der Cochlea, dem Tumorvolumen und der Infiltration der Apertura cochlearis korreliert.

Ergebnisse Es wurden weder Unterschiede zwischen der Signalintensität in Cochlea und Utriculus/Sacculus vor und nach SRS noch eine Korrelation mit klinischen Symptomen, cochleärer Strahlendosis, Tumorvolumen, Koos-Grad oder Infiltration der Cochlea-Apertur festgestellt (alle $p > 0{,}05$).

Schlussfolgerung Die Studie stützt die Theorie einer komplexen Wechselwirkung, die zur Veränderung der Proteinkonzentration der Endolymphe führt, und nicht die direkte Abhängigkeit von der SRS. Diesen Daten zufolge hat die Anwendung moderner Dosierungsschemata einen positiven Einfluss auf das klinische Ergebnis mit Erhalt des Hörvermögens bei VS-Patienten.

Schlüsselwörter 3-D-CISS · Signalverlust Labyrinth · Magnetresonanztomographie · Vestibularisschwannom · Radiochirurgie

Abbreviations

3D-CISS	Three-dimensional constructive interference in steady state
CPA	Cerebellopontine angle
CSF	Cerebrospinal fluid
dB	Decibel
FLAIR	Fluid-attenuated inversion recovery
FoV	Field of view
Gy	Gray
IAC	Internal auditory canal
LVA	Large vestibular aqueduct syndrome
MPR	Multiplanar reconstruction
PTA	Pure-tone audiometry
SRS	Stereotactic radiosurgery
ST	Slice thickness
TE	Echo time
TR	Repetition time
VS	Vestibular schwannoma

Introduction

Vestibular schwannomas (VSs) are benign, slow-growing tumours arising from the nerve sheath of the eighth cranial nerve with an annual incidence between 1.1 and 1.9 per 100,000 [1]. VSs usually occur sporadically, but may also be associated with neurofibromatosis type 2 (NF2). Common symptoms are hearing impairment, tinnitus, dizziness and vertigo; less frequent ones are ataxia, gait disturbance, facial nerve disorders and giant VSs may cause obstructive hydrocephalus. The origin of VS-associated hearing loss, dizziness and vertigo remains unclear and is the subject of controversial debate in the literature. Supporting evidence of its dependence on cochlear or vestibular nerve dysfunction is based on reports of retro-cochlear electrophysiological abnormalities in affected patients [2, 3] and on histopathological studies demonstrating atrophy of the cochlear [4, 5] or vestibular nerve [6, 7] on the affected side. Dysfunctions within the inner ear may offer a further explanation of the VS-associated cochlear and vestibular symptoms. Several histopathological descriptions of VS have noted ipsilateral inner ear alteration such as endolymphatic hydrops and endolymphatic/perilymphatic acidophilic-staining precipitates [8–10]. According to Silverstein et al. [11], the formation of these precipitates seems to be related to the increased protein content on the affected side. Based on the hypothesis of Bhadelia et al. [12] and the results of further studies [13–15], evaluation of increased inner ear protein content in patients with VS can be carried out in vivo and noninvasively by means of dedicated magnetic resonance imaging (MRI) sequences—especially 3D fluid-attenuated inversion recov-

ery (3D-FLAIR) and 3D-constructive interference in steady state (3D-CISS). Although both inner ear signal intensity (in 3D-FLAIR and 3D-CISS) and acidophilic-staining precipitates in histopathological studies are altered on the side affected by VS, the correlation between these findings and cochlear or vestibular symptoms is still weak.

We have previously reported a significant correlation between vertigo and inner ear signal loss in 3D-CISS on the affected side [16]. Miller et al. described an association between cochlear signal in 3D-FLAIR and pretreatment hearing levels [13]. Somers et al. demonstrated a significant association between 3D-CISS in preoperative settings and hearing preservation after surgery [14]. This result was confirmed by Prabhu et al. in their study on a larger patient cohort after radiosurgical treatment [15]. Additionally, Somers et al. found a significant relationship between signal intensity in 3D-CISS and tumour involvement of the fundus of the internal auditory canal (IAC).

There are three main options for the management of VS: the conservative approach with regular MRI check-ups, microsurgery and radiosurgery or fractioned stereotactic radiation therapy. The choice depends on tumour size and symptoms. In our centre, the decision on treatment is made by our interdisciplinary Schwannoma Board. The radiosurgery techniques for treating VSs are extremely accurate and avoid damage to the neighbouring structures thanks to a narrow beam of high-energy photons targeted at the lesion. This approach improves on the traditional stereotactic radiosurgery (SRS) introduced by Leksell [17]. Three types of devices are suitable for this procedure: the Gamma Knife (Elekta AB, Stockholm, Sweden)—characterised by a beam emitted from a cobalt-60 source, linear accelerators (LINACs), and the CyberKnife—a LINAC equipped with a robotic arm applicator (Accuray, Sunnyvale, CA, USA).

According to the guidelines of the Congress of Neurological Surgeons (CNS) concerning the radiotherapeutic management of VSs [18], no particular radiosurgery technique exhibits superiority over the others. For example, Coughlin et al. reported no significant dependency of hearing preservation rate after SRS on radiotherapy modality, fractionation or dose in their systematic review [1]. The CNS was therefore unable to make an outcome-based recommendation about the radiotherapy modality, the number of fractions or the prescription dose for treating VSs. Nevertheless, the CNS suggests using a dose under 13 Gray (Gy) for single-fraction radiosurgery to minimise hearing and cranial nerve deficits.

Taking these findings into account, we compared 3D-CISS sequences before and after primary SRS of unilateral VSs to evaluate the effect of the radiosurgery on the 3D-CISS signal intensities of cochlea and sacculus/utriculus. Additionally, we analysed the correlation between these signal intensities and cochlear radiation dose, clinical symptoms, tumour volume and infiltration of the cochlea aperture.

Materials and methods

This retrospective study was approved by the Ethics Committee of the Canton of Bern (KEK number 2017-02127) and was performed in accordance with the Declaration of Helsinki (2013; [19]).

Patients

The medical records of patients with unilateral VS treated between January 2010 and August 2016 with single-fraction SRS were retrospectively analysed. Patients with pre- and posttreatment MR data sets that included 3D-CISS sequences and complete pretherapeutic and follow-up clinical neuro-otological examination records were included. Patients diagnosed with NF2, aged below 18 years, and those who had had previous surgery and/or fractionated radiotherapy were excluded.

Clinical assessment

Preoperative and postoperative hearing levels were recorded by means of pure-tone audiometry (PTA). We averaged the PTA measures at 0.5 KHz, 1 KHz, 2 KHz and 4 KHz and defined hearing impairment as a mean value greater than 25 decibel (dB) according to the definition of the World Health Organization (WHO; [20–22]). Patients were simply coded as having or not having a hearing impairment. We did not distinguish between levels of hearing impairment. The audiometry was performed before SRS, at the first follow-up and at the last follow-up after radiosurgery. Before SRS the patients were asked to answer binary (yes/no) questions about their subjective symptoms of tinnitus, vertigo and problems with balance. These questions were repeated at the first and last follow-up.

MRI acquisition

We analysed internal and externally performed imaging studies. The necessity for external images was especially due to follow-ups performed in other external institutions. For internal investigations we used a 1.5T or a 3T Siemens scanner (Magnetom Avanto or Magnetom Verio, Siemens Medical Solutions, Erlangen, Germany) with 12-channel head coils and applied our MRI standard temporal bone protocol with 3D-CISS.

The protocol included the following sequences for the native images: axial T1-weighted (T1w) and T2-weighted (T2w) sequences for the whole brain, coronal T2w covering

the temporal bone, axial T1w over the temporal bone, and 3D axial CISS above the temporal bone at the level of the IAC. After contrast applications, the following sequences were acquired: coronal T1w with fat suppression covering the temporal bone, axial T1w with fat suppression above the temporal bone, and 3D T1w MPR sequences over the whole brain. The parameters for the specially analysed 3D-CISS were standardized at 1.5T and 3T; 1.5T: TR 1400 ms, TE 185 ms, ST 0.6 mm, FoV 190 × 190 mm^2 and acquisition time: 4:36 min and 3T: TR 1000 ms, TE 132 ms, ST 0.5 mm, FoV 199 × 199 mm^2 and acquisition time: 4:31 min. The imaging protocol was kept stable for each scanner throughout the acquisition period.

Radiosurgery

The VS were treated by SRS with either 6 MV robotic Cyberknife (Accuray, Sunnyvale, CA, USA) or LINAC (Novalis, Brainlab, Munich, Germany). Patients were immobilised in a supine position on the treatment table using a commercial stereotactic mask fixation system in conjunction with the Multiplan (Accuray, Sunnyvale, CA, USA) and iPlan (Brainlab, Munich, Germany) treatment-planning system. Target volumes and organs at risk were delineated slice by slice in axial view, using postcontrast thin-slice (1-mm) gadolinium-enhanced T1- and T2-weighted axial MRI sequences fused with thin-slice (0.75 mm) planning computed tomography scans (Fig. 1). Target definition and dose prescriptions (12 Gy marginal dose prescribed to a mean isodose line of 88.1%, range 52–99%) were based on international consensus guidelines [23].

Imaging analysis

The evaluation of MRI scans was performed twice for each patient: by a resident in radiology (M.G.) and by a neuroradiologist with extensive experience in head and neck imaging (F.W.) blinded to the clinical data and to the other rater's interpretation. Disagreements on rating of cochlear 3D-CISS signal were recorded and subsequently discussed between the two raters until consensus was achieved.

The tumour size was graded before SRS and at follow-up according to the following institutionally modified Koos classification [24]: Koos stage 1—tumour confined to the IAC; stage 2—tumour extension over the IAC without contact to the brainstem; stage 3—tumour having contact with the brainstem but not compressing it; stage 4a—tumour compressing the brainstem without infratentorial midline shift; stage 4b—tumour compressing the brainstem with infratentorial midline shift. For each patient in our database, we analysed the signal intensity of the cochlea and sacculus/utriculus on 3D-CISS sequences before SRS (usually on the radiotherapy planning data set) and on the last follow-up MRI. For the qualitative visual analysis of the membranous labyrinth in initial and follow-up MR scans we compared the signal intensity of the inner ear (cochlear endolymph and sacculus/utriculus) to the signal intensity of the cerebrospinal fluid (CSF), which should normally be equal in healthy patients. We used simple binary (yes/no) discrimination for verifying loss of signal intensity of the membranous labyrinth compared to the CSF in the initial MRI and in follow-up imaging. The verification of the signal intensity of the inner ear is routinely reported for each schwannoma patient treated at our institution.

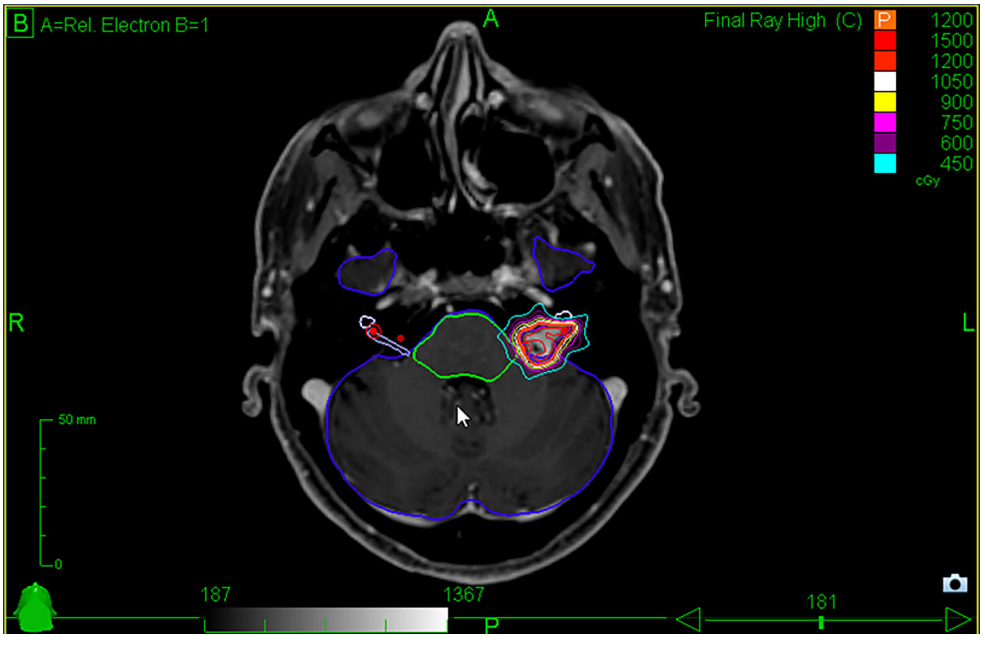

Fig. 1 Example of a Cyberknife plan for a 68-year-old woman with a left VS Koos II treated with 1 × 12 Gy

We always performed a separate analysis for the cochlea, the complex of utriculus and sacculus, and validated the images on a certified reporting station (DIN V 6868-57 and quality assurance guideline).

The anatomical structure of the utriculus and sacculus was reviewed to identify abnormalities and determine the size of the vestibular aqueduct to rule out a concomitant large vestibular aqueduct syndrome (LVA). The tumour infiltration of the cochlear aperture was likewise recorded when present. We measured and identified LVA according to Valvassori et al. ([25]; i.e. a vestibular aqueduct diameter greater than 1.5 mm). Tumour size in millimetres was recorded on the MRI data set before radiotherapy (at diagnosis and during MRI planning) and from the last follow-up MR scan available. Tumour volume in cubic millimetres was measured for each patient before SRS, at the 6-month follow-up and at the last follow-up. For the semi-automatic volumetric tumour measurement, we used 3D Slicer 4.4.0, which is freely downloadable (from the website http://www.slicer.org). 3D Slicer is a personal-computer-based image analysis tool where the region of interest (VS) is manually contoured in each slice; the software then calculates the volume of the contoured region and the total volume is given in cubic millimetres. For all patients, we used the contrast-enhanced 3D T1w multiplanar reconstruction (MPR) sequence for the delineation of the tumour mass.

Statistical analysis

Statistical analysis (D.L.; certified statistician) was used to asses' differences between the signal intensities of cochlea and utriculus/sacculus before and after SRS and their correlation with cochlear doses, clinical symptoms, tumour volume and tumour infiltration of the cochlear aperture. Depending on the type of variables one out of three different non-parametric statistical tests was applied: Kruskal–Wallis rank test, Fisher's exact test or McNemar test. We used the first to analyse the effect of the cochlea doses (mean and maximum dose) on the signal intensity in 3D-CISS after SRS (in both cochlea and utriculus/sacculus). We also applied this test to study the influence of the tumour size (volumetry and Koos grading) on the signal intensities of cochlea and utriculus/sacculus in 3D-CISS both before SRS and at follow-up. Fisher's exact test was used to investigate the correlation of signal intensity in 3D-CISS (cochlea and utriculus/sacculus) with clinical symptoms before SRS, at follow-up and in cross-correlation. Additionally, we used it to analyse the correlation between infiltration of the cochlear aperture before SRS on the signal intensities in 3D-CISS. Using the McNemar test we evaluated the effect of SRS on the signal intensity of cochlea and utriculus/sacculus in 3D-CISS, testing whether the row and column marginal frequencies of the signal intensities before treatment and at follow-up are equal. Statistical analysis was performed using SPSS Statistics Version 24.0 (IBM Corp, Armonk, NY, USA).

Results

Patients' characteristics

Forty-seven patients met the inclusion criteria for this study. Twenty-four (51.1%) were males and 23 (48.9%) females with a median age of 59 years (range 23–78 years) at the time of diagnosis of the VS; the patients' mean age at the time of SRS was 62 years (range 24–80 years). The median duration of MRI follow-up was 29 months (range 6–79 months) after SRS. The median duration of the clinical follow-up was 28 months (range 6–71 months) after SRS. All patients were treated with single-fraction SRS with a prescribed target dose to the tumour of 12 Gy.

Table 1 Patients' demographics, radiological data and radiation dose. The values are expressed as average + standard deviation or percentage

Parameter	Distribution (%)
N° of patients	47
Lesion side	L = 26 (55.3); R = 21 (44.7)
Prescription dose to the tumour (Gy)	12 (100)
Target mean dose (Gy)	Mean ± SD = 13.0 ± 1.2
Target maximum dose (Gy)	Mean ± SD = 13.9 ± 2.3
Cochlea mean dose (Gy)	Mean ± SD = 5.2 ± 2.9
Cochlea maximum dose (Gy)	Mean ± SD = 9.3 ± 3.3
Cochlear aperture infiltration before SRS	22 (46.8)
N° of months SRS to last follow-up MRI	Mean ± SD = 28.7 ± 17.9
Cochlea signal loss before SRS	40 (85.1)
Cochlea signal loss last follow-up MRI	37 (78.7)
Sacculus/utriculus signal loss before SRS	37 (78.7)
Sacculus/utriculus signal loss last follow-up MRI	36 (76.6)

SRS stereotactic radiosurgery, *L* left, *R* right, *SD* standard deviation, *N°* number

Table 2 Koos grade and tumour volume before and after radiosurgery

Parameter		Distribution (%)
Koos grade before SRS	Koos 1	7 patients (14.9)
	Koos 2	22 patients (46.8)
	Koos 3	9 patients (19.1)
	Koos 4a	7 patients (14.9)
	Koos 4b	2 patients (4.3)
Koos grade at last follow-up	Koos 1	10 patients (21.3)
	Koos 2	20 patients (42.5)
	Koos 3	13 patients (27.7)
	Koos 4a	4 patients (8.5)
	Koos 4b	0 patients (0)
Minimum initial tumour size before SRS (mm)	–	4.4 × 4.0 × 3.4
Maximum initial tumour size before SRS (mm)	–	25.0 × 19.8 × 17.2
Minimum tumour size at follow-up (mm)	–	4.8 × 4.1 × 2.3
Maximum tumour size at last follow-up (mm)	–	25.0 × 20.3 × 17.5
Tumour volume before SRS (mm^3)	–	Mean ± SD = 938.8 ± 823.4
Tumour volume at 6-month follow-up (mm^3)	–	Mean ± SD = 1092.2 ± 959.7

SRS stereotactic radiosurgery

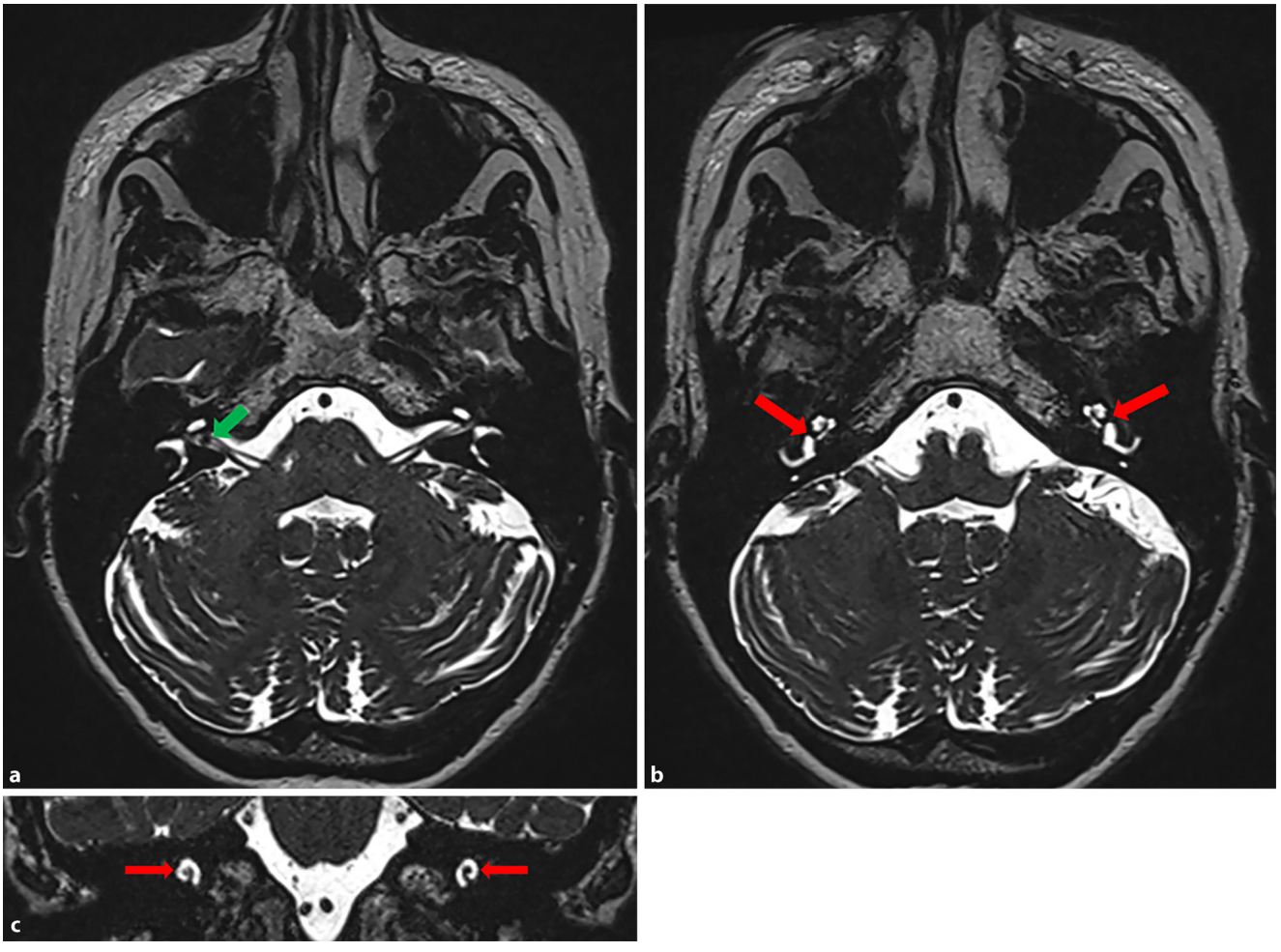

Fig. 2 Fifty-one-year-old woman with vestibular schwannoma Koos I on the right side (**a**; initial MRI; *green arrow*). The axial 3D-CISS (**a** and **b**) and the 3D-CISS coronal reformation (**c**) showed a normal appearance of cochlea and sacculus/utriculus with signal intensity similar to cerebrospinal fluid pretreatment (*red arrows*)

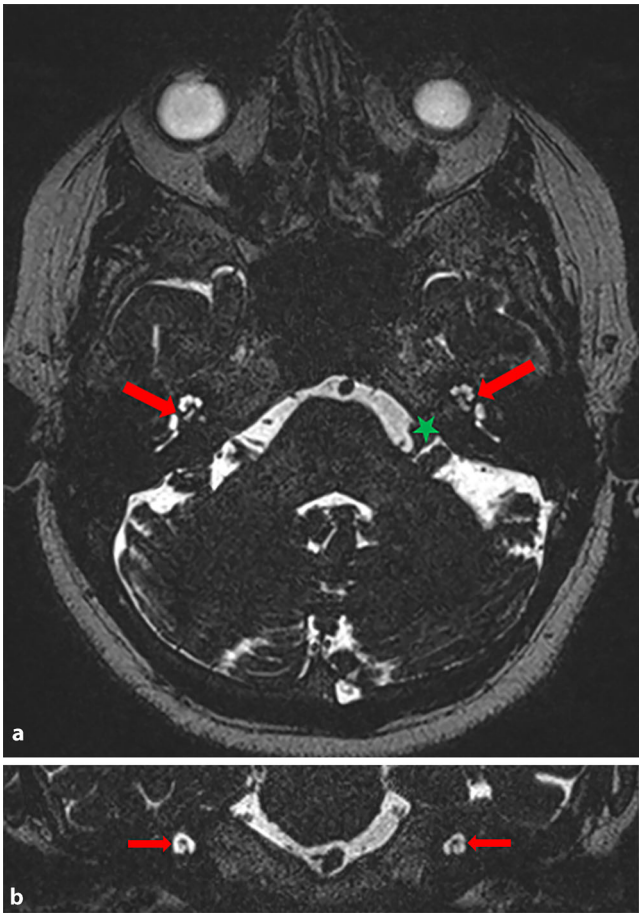

Fig. 3 Sixty-eight-year-old man with vestibular schwannoma Koos II on the left side (**a**; initial MRI; green star). The baseline axial 3D-CISS (**a**) and the 3D-CISS coronal reformation (**b**) revealed a pretreatment signal loss in the cochlea and vestibule (*red arrows*); unchanged 14 month after SRS

Patients' demographic characteristics, results of radiological evaluation and radiation dose are summarised in Table 1. Koos grading and tumour volume before and after SRS are shown in Table 2.

Radiosurgery results

Twenty-eight patients (59.6%) were treated with a Novalis device (LINAC) produced by Brainlab (Feldkirchen, Germany) and 19 patients (40.4%) with the CyberKnife.

On average, the prescribed target overall maximum dose was 13.92 Gy (range 12.12–23.10 Gy) and the target mean dose was 13.00 Gy (range 11.88–17.70 Gy). The maximal and mean dose to the cochlea were 9.27 Gy (range 2.67–13.34 Gy) and 5.22 Gy (range 0.85–10.72 Gy), respectively.

Clinical outcome

We found no correlation between the initial signal intensities of the cochlea before SRS with the patients' subjective hearing problems ($p = 0.571$) or objective hearing impairment ($p = 1.000$). There were no posttreatment correlations at the first follow-up ($p = 0.279$) or at the last follow-up ($p = 0.195$) of objective hearing impairment with the cochlea signal intensity pretreatment. The cochlear signal intensities at the last follow-up after SRS were not correlated with the audiometry-verified hearing impairment ($p = 0.075$).

The signal intensities of sacculus and utriculus before SRS were not associated with tinnitus in general ($p = 0.460$). Neither acute onset of posttreatment tinnitus ($p = 0.711$) nor progressive tinnitus during the clinical course posttreatment ($p = 0.706$) were correlated to the signal intensity of utriculus/sacculus before SRS. In patients who complained of progressive tinnitus at the last clinical follow-up no correlation to the signal of the sacculus/utriculus at the last follow-up MR scan after SRS ($p = 0.706$) was seen. Vertigo before SRS ($p = 1.000$), acute-onset vertigo posttreatment ($p = 0.444$) and progressive vertigo during clinical course posttreatment ($p = 0.477$) were not correlated to an initial signal drop of sacculus/utriculus before SRS. There was also no correlation between progressive vertigo after SRS and the signal intensities of sacculus and utriculus after treatment ($p = 1.000$). After SRS, neither subjective acute balance problems ($p = 0.164$) nor progressive balance problems ($p = 0.263$) showed any correlation to the initial signal intensity of the sacculus/utriculus. At the last consultation after SRS, progressive subjective balance problems ($p = 0.263$) were not correlated to the hypointense signal of the sacculus/utriculus after SRS.

Imaging results

Signal intensity in 3D-CISS, radiation dose and symptoms

At the initial MRI, the cochlea appeared normal with signal intensity corresponding to cerebrospinal fluid in 7 patients (14.9%; Fig. 2). In 40 patients (85.1%) obliteration of the cochlea with signal drop was present in the 3D-CISS on the side with the tumour (Fig. 3). In 37 of these patients, obstruction of the cochlea as well as loss of signal in sacculus and utriculus was reported (92.5%; respectively 37 of 47 [78.7%]) on the side with the tumour (Fig. 3). In none of the patients was a signal loss of the membranous labyrinth verified on the contralateral normal side. Sequential analysis of the follow-up MRI series showed a slightly decreased rate of obliteration of the labyrinth. At the last follow-up MR scan, post-SRS, hypointense signal of the cochlea was retained in 34 of the 40 patients in whom it was noted pretreatment (72.3%; respectively in 37 of all 47 [87.7%]). The

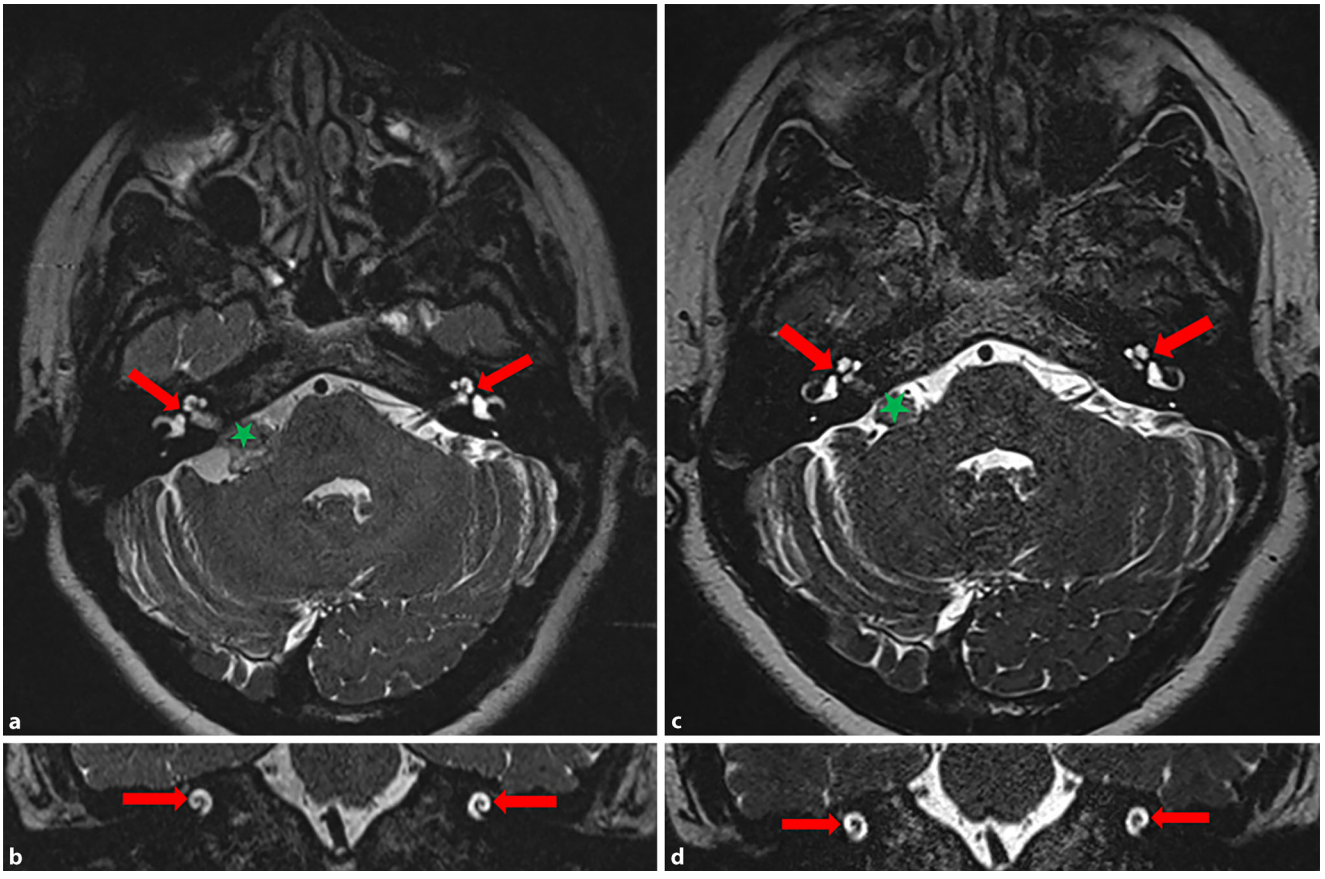

Fig. 4 Fifty-year-old woman with vestibular schwannoma Koos III on the right side (**a**; initial MRI; *green star*). The baseline axial 3D-CISS (**a**) and the baseline 3D-CISS coronal reformation (**b**) showed a signal drop of the cochlea (*red arrows*) and sacculus/utriculus with hypointense signal intensity compared to cerebrospinal fluid. The follow-up MRI with axial 3D-CISS (**c**) and 3D-CISS coronal reformation (**d**) 25 months after stereotactic radiotherapy revealed a signal intensity of the cochlea equivale to CSF and thus normal (*red arrows*)

follow-up MR scan for 6 of the 40 patients (12.8%) with initial signal drop of the cochlea revealed normalisation of the signal intensity of the inner ear; equal to the signal intensity of the CSF as normal. At the last follow-up, MRI loss of signal into sacculus/utriculus was still present in 32 of the 37 patients in whom it was initially documented (86.5%, respectively in 36 of all 47 [76.6%]; Fig. 4). All patients had a normal configuration of utriculus and sacculus without any anatomical anomalies and no patients had an LVA.

Statistical analysis revealed no significant differences between the signal intensities of cochlea and utriculus/sacculus before and after SRS ($p = 0.508$ and $p = 1.000$) and their correlation with cochlear doses, clinical symptoms, tumour volume and tumour infiltration of the cochlear aperture. All statistical analyses (Kruskal–Wallis rank test, Fisher's exact test and McNemar test) resulted in a p-value greater than 0.05 and were therefore not statistically significant.

A complete overview of the results of our analysis is provided in Table 3.

Discussion

The 3D-FLAIR and 3D-CISS MRI sequences provide a visual representation of the inner ear in which the signal intensity is supposed to be an indicator of the endolymph's protein content [12, 15]. It is suggested that protein interactions may have an impact on the preservation of posttreatment hearing outcome in VS patients treated with SRS. Additional support for the labyrinthine protein disturbance theory comes from MRI signal abnormality. Protein sensitivity has recently been tested in 3D-CISS by Prabhu et al. [15]; who demonstrated that cochlear signal before treatment was not associated with pretreatment hearing level. They concluded that hearing loss in patients with reduced hearing preoperatively must be multifactorial and affected by other factors independent of 3D-CISS signal or labyrinthine protein concentration, such as neuronal or vascular compression or age-related hearing deterioration. In line with the results of Prabhu et al. [15] we did not find any influence of the SRS on the signal intensities of the cochlea or utriculus/sacculus when we compared the intensities before and after therapy as well as the subjective and objective hearing

Table 3 Statistical analysis comparing the clinical symptomatology, tumour volume, Koos grade and cochlear aperture infiltration versus the initial and follow-up obstruction of the inner ear (MRI drop of signal in the cochlea and vestibule)

Parameter	Signal intensity in 3D-constructive interference into steady state (3D-CISS)					
	Cochlea signal intensity before SRS	Cochlea signal intensity at last follow-up	Sacculus/utriculus signal intensity before SRS	Sacculus/utriculus signal intensity at last follow-up	Difference between cochlea signal intensity before SRS and at last follow-up	Difference between sacculus/utriculus signal intensity before SRS and at last follow-up
Subjective hearing problems before SRS	P = 0.571	–	–	–	–	–
Objective hearing impairment before SRS	$p = 1.000$	–	–	–	–	–
Objective hearing impairment at first follow-up after SRS	$p = 0.279$	–	–	–	–	–
Objective hearing impairment at last follow-up after SRS	$p = 0.195$	$p = 0.075$	–	–	–	–
Tinnitus before SRS	–	–	$p = 0.460$	–	–	–
Acute tinnitus after SRS	–	–	$p = 0.711$	–	–	–
Progressive tinnitus after SRS	–	–	$p = 0.706$	$p = 0.706$	–	–
Vertigo before SRS	–	–	$p = 1.000$	–	–	–
Acute vertigo after SRS	–	–	$p = 0.444$	–	–	–
Progressive vertigo after SRS	–	–	$p = 0.477$	$p = 1.000$	–	–
Acute balance problems after SRS	–	–	$p = 0.164$	–	–	–
Progressive balance problems after SRS	–	–	$p = 0.263$	$p = 0.263$	–	–
Mean cochlear dose (Gy)	–	$p = 0.391$	–	$p = 0.366$	$p = 0.939$	$p = 0.899$
Maximum cochlear dose (Gy)	–	$p = 0.181$	–	$p = 0.187$	$p = 0.779$	$p = 0.635$
Tumour volume before SRS	$p = 0.229$	–	$p = 0.287$	–	–	–
Tumour volume at last follow-up after SRS	–	$p = 1.000$	–	$p = 0.688$	–	–
Koos grade before SRS	$p = 0.241$	–	–	–	–	–
Koos grade at last follow-up after SRS	–	$p = 0.847$	–	–	–	–
Cochlear aperture infiltration before SRS	$p = 1.000$	–	$p = 1.000$	–	–	–

SRS stereotactic radiosurgery

outcome and the clinical characteristics evaluated at initial consultation, pretreatment and at final follow-up after SRS (Table 3). The signal loss of the inner ear structures on the affected side was independent of the mean and maximum cochlear radiation dose ($p > 0.180$). Interestingly, the follow-up scan of 6 of the 40 patients (12.8%) with initial signal drop of the cochlea and 5 of the 37 patients (13.5%) with initially documented hypointensity of the sacculus/utriculus revealed a normalisation of the signal intensity of the inner ear; similar to the normal CSF signal and rated as normal. It is known that endogenous cellular regeneration does not occur in the human inner ear and there is no exogenous therapy that can replace damaged hair cells. Several reasons might explain the decreased protein concentration in endolymph and perilymph in association with VS: (1) Breakdown of the blood-endolymph/perilymph barrier initially caused by either high venous pressure or arterial stasis; (2) Impairment of the endolymph and perilymph turnover caused by blockage of the cochlear aqueduct by the tumour; (3) Blockage of neuroaxonal transport of proteins by compression of the cochlear nerve; and (4) Cell-mediated immune response to tumour antigens [12, 26, 27]. There might be minimal changes in as yet unknown factors that exert a significant influence on the signal characteristic of the inner ear. Further investigations are needed on possible inner ear regeneration. Objective, region of interest-based quantitative assessment of the 3D-CISS signal of the inner ear by calculating the unique ion transport (potassium concentration [K^+] and sodium concentration [Na^+]) would be valuable.

As explained in previous studies, the changes in the signal intensity in 3D-CISS can be considered a marker for changes of the inner ear protein content, which in turn represent a pathological alteration in patients with VS [11, 28]. The absence of significant effects of the SRS on the signal intensities of cochlea and utriculus/sacculus in 3D-CISS support the low side-effect profile of SRS for the treatment of VS, independent of the cochlear dose when a prescribed dose of 12 Gy is administered.

Furthermore, Somers et al. [14] and Prabhu et al. [15] demonstrated a correlation between the pretreatment hypointense signal intensity of the cochlea and the posttherapeutic hearing outcome in patients affected with VS and treated with surgery or SRS. Accordingly, they postulated a predictive value of the cochlear hypointense signal for the hearing outcome after surgery or SRS. By contrast, our results did not show any correlation of the clinical parameters analysed with the signal intensity of the cochlea or utriculus/sacculus in 3D-CISS either before or after radiosurgery. Therefore, our results do not support a predictive function of the cochlear signal intensity in 3D-CISS for posttherapeutic hearing outcome.

The reason for the differing results between these three studies could be the different definitions of hearing preservation and the statistical tests chosen for the data interpretation. Somers et al. [14] defined hearing preservation as an average PTA (between PTA at 0.5, 1, 2 and 4 KHz) >50 dB with <30 dB of intraneural difference with a concurrent tumour extension into the posterior fossa <20 mm and a speech discrimination score >70%. Prabhu et al. [15] used the scale developed by the American Association of Otolaryngology–Head and Neck Surgery. Our classification was based on the WHO definition, with a threshold of 25 dB [20–22]. For the statistical analyses we used Fisher's exact test instead of the chi-square test. We are aware that Fisher's exact test is more conservative than the chi-square test. For the chi-square test to give a correct value, certain conditions must be met (e.g. less than 20% of the cells should have an expected frequency of <5 and no cell should have an expected frequency of <1). The distribution of our data justified our choice of the Fisher test since it did not meet the requirements for applying an approximation method like the chi-square test but required an exact statistical test [29].

A further distinction between our results and those of Somers et al. [14] is the lack of correlation between the signal intensity of the cochlea and utriculus/sacculus with the infiltration of the cochlear aperture ("fundus" in Somers et al. [14]).

Furthermore, in this study of patients exclusively treated with SRS, we were not able to confirm our previous findings of a correlation between a hypointense signal of the utriculus/sacculus and vertigo ([16]; $p > 0.400$ in the present analysis); at that time no pure radiotherapy cohort was available.

Another important consideration is the subjective visual analysis and interpretation of the intensities of cochlea and utriculus/sacculus. In our study the two reviewers performed the visual assessment of the signal intensity of the inner ear independently and came to an agreement on patients they had rated differently. The two blinded reviewers had greater than 90% initial agreement in rating symmetry. However, the rating of the signal intensity of the inner ear in 3D-CISS is always dependent on the experience of the (neuro-)radiologist and will inevitably be more accurate in centers that specialize in the management of VS patients.

In summary, this study revealed that SRS for treatment of VS has no influence on the signal intensities of cochlea and sacculus/utriculus, independent from the cochlear mean and maximum dose when a prescription dose of 12 Gy is the target. We can infer that SRS for treatment of VS with a prescribed target dose of 12 Gy does not provoke any pathological endolymphatic changes observable in 3D-CISS at follow-up. Furthermore, our results do not confirm the value of the cochlear intensity in 3D-CISS before treatment as a predictor for the hearing outcome after SRS as

hypothesized in earlier studies; in our analysis no correlation between signal intensities of inner ear structures and symptoms was evident.

Limitations

Owing to the retrospective nature of this study, for a few individual patients the follow-up audiometry data and follow-up measurements concerning the three parameters tinnitus, vertigo and balance problems were not recorded for long-term MRI follow-up and we could only evaluate the 6-month follow-up MR scan. The time variance of follow-up MRIs was also relatively wide; while some patients moved quickly to ambulant medical treatment, others appreciated the connection to the university aftercare service and attended for regular check-ups by our Schwannoma Board.

Conclusion

Our investigation supports the theory of a complex interaction of diverse factors causing the alteration of the endolymph protein concentration on the affected side and no direct dependency on the type of treatment (especially radiosurgery), tumour size or on the infiltration of the cochlear aperture. In our opinion, using modern dosing schemes will have a positive impact on clinical outcome in VS patients with preserving hearing. Furthermore, future investigations will need to assess objective, region of interest-based quantitative assessment of 3D-CISS signal of the inner ear by calculating the unique ion (K^+ and Na^+) transports.

Compliance with ethical guidelines

Conflict of interest F. Wagner, M. Gandalini, A. Hakim, E. Ermis, D. Leiser, M. Zbinden, L. Anschuetz, A. Raabe, M. Caversaccio, R. Wiest and E. Herrmann declare that they have no competing interests.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Coughlin AR, Willman TJ, Gubbels SP (2018) Systematic review of hearing preservation after radiotherapy for vestibular schwannoma. Otol Neurotol 39:273–283
2. Selters WA, Brackmann DE (1977) Acoustic tumor detection with brain stem electric response audiometry. Arch Otolaryngol 103:181–187
3. Grayeli AB, Refass A, Smail M, Elgarem H, Kalamarides M, Bouccara D, Sterkers O (2008) Diagnostic value of auditory brainstem responses in cerebellopontine angle tumours. Acta Otolaryngol 128:1096–1100
4. Eckermeier L, Pirsig W, Mueller D (1979) Histopathology of 30 non-operated acoustic schwannomas. Arch Otorhinolaryngol 222:1–9
5. Johnsson LG, Hawkins JE, Rouse RC (1984) Sensorineural and vascular changes in an ear with acoustic neurinoma. Am J Otolaryngol 5:49–59
6. Benitez JT, Lopez-Rios G, Novoa V (1967) Bilateral acoustic neuroma. A human temporal bone report. Arch Otolaryngol 86:25–31
7. Merchant SN, Nadol JB, Schuknecht HF (2010) Schuknecht's pathology of the ear. McGraw-Hill, New York
8. De Moura LF (1967) Inner ear pathology in acoustic neurinoma. Arch Otolaryngol 85:125–133
9. Mahmud MR, Khan AM, Nadol JB (2003) Histopathology of the inner ear in unoperated acoustic neuroma. Ann Otol Rhinol Laryngol 112:979–986
10. Roosli C, Linthicum FH, Cureoglu S, Merchant SN (2012) Dysfunction of the cochlea contributing to hearing loss in acoustic neuromas: an underappreciated entity. Otol Neurotol 33:473–480
11. Silverstein H, Schuknecht HF (1966) Biochemical studies of inner ear fluid in man. Changes in otosclerosis, Meniere's disease, and acoustic neuroma. Arch Otolaryngol 84:395–402
12. Bhadelia RA, Tedesco KL, Hwang S, Erbay SH, Lee PH, Shao W, Heilman C (2008) Increased cochlear fluid-attenuated inversion recovery signal in patients with vestibular schwannoma. AJNR Am J Neuroradiol 29:720–723
13. Miller ME, Mafee MF, Bykowski J, Alexander TH, Burchette RJ, Mastrodimos B, Cueva RA (2014) Hearing preservation and vestibular schwannoma: Intracochlear FLAIR signal relates to hearing level. Otol Neurotol 35:348–352
14. Somers T, Casselman J, de Ceulaer G, Govaerts P, Offeciers E (2001) Prognostic value of magnetic resonance imaging findings in hearing preservation surgery for vestibular schwannoma. Otol Neurotol 22:87–94
15. Prabhu V, Kondziolka D, Hill TC, Benjamin CG, Shinseki MS, Golfinos JG, Roland JT Jr, Fatterpekar GM (2018) Preserved cochlear CISS signal is a predictor for hearing preservation in patients treated for vestibular schwannoma with stereotactic radiosurgery. Otol Neurotol 39:628–631
16. Wagner F, Herrmann E, Wiest R, Raabe A, Bernasconi C, Caversaccio M, Vibert D (2018) 3D-constructive interference into steady state (3D-CISS) labyrinth signal alteration in patients with vestibular schwannoma. Auris Nasus Larynx 45:702–710
17. Leksell L (1951) The stereotaxic method and radiosurgery of the brain. Acta Chir Scand 102:316–319
18. Germano IM, Sheehan J, Parish J, Atkins T, Asher A, Hadjipanayis CG, Burri SH, Green S, Olson JJ (2018) Congress of Neurological Surgeons systematic review and evidence-based guidelines on the role of radiosurgery and radiation therapy in the management of patients with vestibular schwannomas. Neurosurgery 82:E49–E51
19. World Medical Association (2013) World medical association declaration of helsinki: ethical principles for medical research involving human subjects. JAMA 310:2191
20. World Health Organization (2014) Deafness prevention. World Health Organization, Geneva (available at: http://www.who.int/deafness/en/)
21. Mathers C, Smith A, Concha M (2003) Global burden of hearing loss in the year 2000. World Health Organization, Geneva, pp 1–30
22. Von Gablenz P, Holube I (2015) Prävalenz von Schwerhörigkeit im Nordwesten Deutschlands: Ergebnisse einer epidemiologischen Untersuchung zum Hörstatus (HÖRSTAT). HNO 63:195–214
23. Tsao MN, Sahgal A, Xu W, De Salles A, Hayashi M, Levivier M, Ma L et al (2017) Stereotactic radiosurgery for vestibular schwan-

noma: International Stereotactic Radiosurgery society (ISRS) Practice guideline. J Radiosurg SBRT 5:5–24
24. Koos W, Spetzler R, Böck F (1976) Microsurgery of cerebellopontine angle tumors. In: Koos W, Spetzler R, Böck F (eds) Clinical microneurosurgery. Thieme, Stuttgart, pp 91–112
25. Valvassori GE, Clemis JD (1978) The large vestibular aqueduct syndrome. Laryngoscope 88:723–728
26. Thomsen J, Saxtrup O, Tos M (1982) Quantitated determination of proteins in perilymph in patients with acoustic neuromas. ORL J Otorhinolaryngol Relat Spec 44:61–65
27. Rasmussen N, Bendtzen K, Thomsen J, Tos M (1984) Antigenicity and protein content of perilymph in acoustic neuroma patients. Acta Otolaryngol 97:502–508
28. Hızlı Ö, Cureoglu S, Kaya S, Schachern PA, Paparella MM, Adams ME (2016) Quantitative vestibular labyrinthine otopathology in temporal bones with vestibular schwannoma. Otolaryngol Head Neck Surg 154:150–156
29. Kim H-Y (2017) Statistical notes for clinical researchers: chi-squared test and Fisher's exact test. Restor Dent Endod 42:152