Published in final edited form as:

Eur Radiol. 2016 March ; 26(3): 849–857. doi:10.1007/s00330-015-3895-9.

3D quantitative assessment of response to fractionated stereotactic radiotherapy and single-session stereotactic radiosurgery of vestibular schwannoma

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Abstract

Objectives—To determine clinical outcome of patients with vestibular schwannoma (VS) after treatment with fractionated stereotactic radiotherapy (FSRT) and single-session stereotactic radiosurgery (SRS) by using 3D quantitative response assessment on MRI.

Materials—This retrospective analysis included 162 patients who underwent radiation therapy for sporadic VS. Measurements on T1-weighted contrast-enhanced MRI (in 2-year post-therapy intervals: 0–2, 2–4, 4–6, 6–8, 8–10, and 10–12 years) were taken for total tumour volume (TTV) and enhancing tumour volume (ETV) based on a semi-automated technique. Patients were

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Electronic supplementary material The online version of this article (doi:10.1007/s00330-015-3895-9) contains supplementary material, which is available to authorized users.

Institutional Review Board approval was obtained. Written informed consent was waived by the Institutional Review Board. Some study subjects or cohorts have been previously reported in the study by Kapoor et al. (*Int. J. Radiation Oncology Biol. Phys.*, 2011).

Methodology: retrospective, diagnostic or prognostic study, performed at one institution.

considered non-responders (NRs) if they required subsequent microsurgical resection or developed radiological progression and tumour-related symptoms.

Results—Median follow-up was 4.1 years (range: 0.4–12.0). TTV and ETV decreased for both the FSRT and SRS groups. However, only the FSRT group achieved significant tumour shrinkage ($p < 0.015$ for TTV, $p < 0.005$ for ETV over time). The 11 NRs showed proportionally greater TTV (median TTV pre-treatment: 0.61 cm^3 , 8–10 years after: 1.77 cm^3) and ETV despite radiation therapy compared to responders (median TTV pre-treatment: 1.06 cm^3 ; 10–12 years after: 0.81 cm^3 ; $p = 0.001$).

Conclusion—3D quantification of VS showed a significant decrease in TTV and ETV on FSRT-treated patients only. NRs had significantly greater TTV and ETV over time.

Keywords

Magnetic resonance imaging; Vestibular schwannoma; Radiotherapy; Gamma Knife radiosurgery; Benign neoplasms

Introduction

Vestibular schwannomas (VS) are benign, slow-growing tumours that arise from the perineural Schwann cells of the superior or inferior vestibular branch of cranial nerve VIII [1]. Typical locations of these tumours are the internal auditory canal (IAC) and/or the cerebellopontine angle.

Treatment decisions are based on the patient's age, severity of symptoms, tumour size, impact on adjacent structures, multiplicity, growth rate, concurrent hydrocephalus and aetiology (sporadic vs. neurofibromatosis type 2; NF2) [2, 3]. Treatment modalities include: (1) wait and see – routine imaging and close observation, (2) partial or total microsurgical resection or (3) radiotherapy [2, 4, 5]. For poor surgical candidates or patients who do not wish to undergo surgical resection, radiotherapy is the only option to achieve local tumour control, preserve hearing and avoid morbidity of the facial and trigeminal nerves [6–8]. The goal of radiotherapy, which includes single-session stereotactic radiosurgery using Gamma Knife (GK) or fractionated stereotactic radiotherapy (FSRT), is to halt tumour progression by inducing necrosis, and to preserve neurological function [9–12].

Along with clinical signs and symptoms, magnetic resonance imaging (MRI) every 1–2 years is used to assess the radiotherapy response based on changes in tumour size and contrast enhancement. VS usually show a strong enhancement after contrast injection, because the blood-brain-barrier is completely absent in extra-axial tumours. Therefore, gadolinium-based MRI is the gold standard for diagnosis and follow-up of VS. After radiotherapy, loss of central enhancement is frequently observed [13, 14].

Transient enlargement of VS after radiation therapy is also a well-known phenomenon and it is essential to distinguish temporary tumour swelling from therapy failure, especially because volume changes may be subtle in VS. Guidelines from 1995 and 2001, recommending linear planimetric measurements of the maximum tumour diameter on axial images, are of limited value in tumour size assessment due to the complex, non-spheroidal

shape of many VS [15–19]. Therefore, radiotherapists often favour methods that can calculate the three-dimensional (3D) tumour volume instead. It has been shown that for small tumours, use of a 3D-measurement method is essential to calculate the true extent of the tumour volume which, in turn, correlates with clinical symptoms on baseline and reflects tumour response to therapy [18]. However, the clinical workflow is often limited because the volume measurements are made manually using contouring of the tumour on each axial MRI slice to build a volume, requiring a substantial amount of post-processing time [10, 18, 20–25]. A precise and work-flow efficient method for tumour volume measurement would be beneficial.

In this study, we present a novel 3D semi-automatic software that can measure the total tumour volume (TTV) and contrast-enhancing tumour volume (ETV) in a workflow-efficient manner. This was done for patients with unilateral VS before and after treatment with GK or FSRT. We hypothesize that non-responders (NRs) to therapy would show tumour growth or less tumour volumetric regression than responders (Rs).

Methods

Study cohort

This single-centre retrospective study was approved by the Institutional Review Board and was US Health Insurance Portability and Accountability Act compliant. Patient consent requirements were waived for this retrospective study. From January 2003 through December 2013, 1,513 patients with VS were treated at our institution, of whom 162 met the inclusion criteria (Fig. 1). Abstracted data included demographics, symptoms at baseline and follow-up, and TTV/ETV (technique described below).

Of the 162 patients, 40 underwent GK therapy and 122 patients were treated with FSRT. Median age at diagnosis was 63 years for GK patients (range 39–85 years, SD 12.35) and 56 years for FSRT patients (range 30–88 years, SD 10.58). The GK group consisted of 22 females and 18 males, whereas the FSRT group included 57 women and 65 men.

Follow-up was defined as time from the last radiation therapy session to the date of the most recent MRI study obtained in our institution. When the patient's treatment changed (surgical resection or second course of radiation therapy), follow-up was discontinued.

Radiation treatment

Single-session radiosurgery was performed using Leksell Gamma Knife[®] Model CTM (Elekta AB, Stockholm, Sweden) according to the standards defined by Flickinger et al. [26]. Fractionated stereotactic radiotherapy was linear accelerator-based, either using the Brainlab (Brainlab AG, Feldkirchen, Germany) or Pinnacle (Philips Healthcare, Andover, MA, USA) treatment planning system. FSRT (2,500 cGy over five sessions prescribed to the 80 % isodose line) was the standard approach at our institution until 2007/2008.

Treatment decisions were made according to our initial analysis of outcome data and by patient's preference. In order to evaluate treatment response, patients were considered as NRs or Rs. To date, there is no guideline or consensus in the literature on the definition of

NRs or Rs [27]. From a clinical perspective, it seems reasonable not only to include radiographic outcomes ('local tumour control') but also clinical information ('freedom from surgical resection' or 'stable clinical status') [27–29]. Therefore, we decided to define patients who required subsequent microsurgical resection or who showed radiological progression and additionally developed new or progressive symptoms as NRs. Radiological progression was defined as when tumour volume at last follow-up MRI was more than double the initial tumour volume. Patients who showed radiological progression but did not develop new or progressive symptoms were considered as Rs.

Imaging studies

MRI studies were obtained on a 1.5 T (84.7 %; GE, Siemens, or Philips) or 3 T scanner (15.3 %; Siemens or Philips). Median time between pre-treatment MRI and start of radiation therapy was 6 days (range 0 days–2.7 years). Median follow-up was 5.3 years for the FSRT group (range 0.5–12.0 years) and 1.7 years for the GK group (range 0.4–8.4 years). Two-year follow-up intervals were calculated for each patient and available MRI studies were matched with biennial intervals (0–2, 2–4, 4–6, 6–8, 8–10 and 10–12 years post-therapy). The last MRI study per period was used for volumetric analysis (described below).

The standard MRI protocol included native axial T2-weighted (T2-w) turbo-spin echo (TSE) and axial T1-weighted (T1-w) TSE sequences through the IAC together with 3D T2-w sequences. Following gadolinium-injection, axial and coronal T1-w TSE sequences were acquired. Optional imaging included axial and coronal fat-saturated T1-w TSE sequences and a 3D Constructive Interference in Steady State sequence. Matrix sizes, slice thicknesses (1–3 mm), and repetition times/echo times for the different scanners varied and were not standardized.

Volumetric analysis

A software prototype (Medisys, Philips Research, Suresnes, France) was used to perform 3D semi-automated quantitative assessment of TTV and ETV, taking about 1 min per examination, at baseline and at all follow-up MRIs. In the first step of analysis, one reader (T.S., 1 year's experience in neuroradiology) who was trained in the software segmented the lesion in 3D. On implementation, this was done by an interactive mouse click and drag within the lesion on one axial Gadolinium-enhanced slice. By employing non-Euclidean radial basis functions, a 3D segmentation mask was generated (Figs. 2a and b). Edits to the 3D segmentation could be made in the same way. With a 3D segmentation and knowing image matrix dimensions and slice thicknesses, TTV could be visualized and calculated (expressed in cm^3 ; Fig. 2c). In order to distinguish between enhancing and non-enhancing tumour portions within the segmented volume, a cubic region of interest (ROI; 1 cm^3) was placed on the pons, a visually non-hyperenhancing area. The software calculated the mean brightness value (MBV) and $\text{MBV} \pm 2 \text{ SD}$ was selected as the threshold, with all values above seen as real contrast enhancement. A 3D colour map was automatically overlaid onto the segmented schwannoma lesion. Blue represented areas with equal or lower signal intensity compared to the $\text{MBV} \pm 2 \text{ SD}$, while all signals exceeding this value were coded in colour shades (aqua – yellow – red), with red representing the maximum signal intensity/

enhancement (Fig. 2d) [30]. The resulting ETV was then expressed in cm^3 of the previously assessed TTV.

The segmentation and enhancement quantification techniques were established in earlier studies [30–36]. Nevertheless, to demonstrate the measurement precision of the software, we scanned various fruits of different sizes (blueberry, strawberry, kiwi, apple and avocado) and applied the same segmentation method described above to the respective T2-w MRI of the fruit (Table 1 and Fig. 1 in the electronic supplementary material).

Statistical analysis

Statistical calculations were performed using SPSS Statistics®, Version 20 (IBM® 2011, Armonk, NY, USA). The method of generalized estimating equations (GEE) was used for longitudinal analysis of TTV and ETV in VS patients. Differences at baseline TTV of GK and FSRT patients were determined using the Mann Whitney U-test. A p -value <0.05 was considered statistically significant.

Results

Study population and treatment characteristics

The main symptoms for radiation treatment referral were increasing tumour size documented by serial imaging and progression of symptoms (hearing loss (90.1 %), tinnitus (56.8 %), imbalance (33.3 %), headaches (31.5 %), vertigo/dizziness (29.0 %) and facial nerve symptoms (13.6 %)). The majority of lesions were homogeneous without cystic changes and there was no predilection for either side (Table 1).

Acute therapy-related complications occurred in five patients in the FSRT group (4.1 %) only and included hair loss ($n = 3$), severe otalgia ($n = 1$) and sicca symptoms ($n = 1$). With a median interval of 7 months, three patients (1.9 % including two FSRT and one GK patient) developed hydrocephalus needing ventriculoperitoneal shunt implantation. To date, no secondary neoplasm arose as a result of the radiation exposure. Patient and treatment characteristics are given in Table 1.

Imaging results (GK patients)

The median baseline TTV of patients treated with GK was 1.03 cm^3 (range $0.17\text{--}8.52 \text{ cm}^3$), enlarging to 1.61 cm^3 (range $0.10\text{--}8.21 \text{ cm}^3$) during the first follow-up (0–2 years after radiosurgery, $p = 0.001$). Follow-up 2–4 years (median TTV: 1.11 cm^3 , range $0.23\text{--}8.41 \text{ cm}^3$) and 4–6 years (median TTV: 1.03 cm^3 , range $0.27\text{--}2.12 \text{ cm}^3$) after GK treatment again revealed a median TTV shrinkage, but the difference between median preprocedural TTV and median TTV 6 years afterwards was not statistically significant. A volume reduction between baseline and last follow-up MRI was observed in 20 patients (50.0 %) with a median decrease in TTV of 0.30 cm^3 (range $0.01\text{--}2.80 \text{ cm}^3$). On baseline and follow-up imaging, homogeneous lesions were constantly smaller than heterogeneous lesions ($p = 0.001$). Over time, values for ETV showed a similar trend to TTV values. However, the percentage of enhancing VS volume was nearly constant, with no significant change (pre-

treatment: 87.1 %; 0–2 years: 83.5 %, 2–4 years: 85.8 %; and 4–6 years: 87.7 %). TTV and ETV changes are outlined in Fig. 3.

Imaging results (FSRT patients)—The median TTV for the 122 patients was 0.96 cm³ (range 0.11–23.48 cm³) before they underwent FSRT. Similar to the GK-group, TTV was highest 0–2 years post-radiation (median TTV: 1.51 cm³; range 0.22–23.87 cm³) and then continuously decreased up to 8–10 years (median TTV: 0.73 cm³; range 0.06–2.65 cm³) after treatment. Ten to 12 years after therapy, median VS volume again increased to 0.81 cm³, which might be related to low patient numbers ($n = 9$). There was a statistically significant shrinkage of VS 2–12 years post FSRT, when compared to baseline and first follow-up MRI (0–2 years after treatment, $p < 0.015$ for all time points), which is shown in Fig. 4. In 81 patients (66.4 %), a TTV reduction was seen between baseline and last follow-up MRI with a median shrinkage of 0.70 cm³ (range 0.00–20.82 cm³). In addition, homogeneous lesions were constantly smaller than heterogeneous lesions at all time points ($p = 0.015$). The ETV of FSRT patients over time showed the same characteristics as TTV. The median percentage of enhancing VS volume was highest at baseline imaging (94.20%, range 9.95–100.00 %) and continually dropped after treatment (8–10 years after FSRT: 85.13 %, range 50.00–100.00 %, $p = 0.460$). Figure 5 shows TTV and ETV outcome over a 10-year interval in a 56-year-old male patient with the first row demonstrating semi-automated VS segmentation on the original MRI slices. The second row represents the 3D model and the third row the quantitative enhancement.

No differences in baseline TTV between the GK and FSRT group were observed ($U = 2270.5$, $p = 0.510$). When comparing the behaviour of GK-treated VS and FSRT-treated VS, significant differences were observed. During follow-up, patients who underwent GK radiosurgery showed proportionally less tumour shrinkage ($p = 0.013$) and less loss of contrast-enhancing volume ($p = 0.020$). For both the total cohort and the GK and FSRT groups there were no differences in terms of sex, lesion side and age group.

Outcome

Following the criteria for distinguishing clinical Rs from NRs to radiation therapy, 11 patients were classified as NRs, including 6.6 % of FSRT patients ($n = 8/122$) and 7.5 % of GK patients ($n = 3/40$). Taken together, subsequent microsurgical resection was performed in four patients (median time from irradiation to surgery: 3.08 years, range 2.25–5.17 years) and radiological progression with new symptoms occurred in seven patients. There was a highly significant difference between clinical Rs and NRs in terms of median TTV: NRs showed increasing median tumour growth over time (pre-treatment: 0.61 cm³; 0–2 years: 1.43 cm³; 2–4 years: 1.25 cm³; 4–6 years: 1.23 cm³; 6–8 years: 1.96 cm³; 8–10 years: 1.77 cm³), whereas proportional tumour shrinkage was observed for Rs (pre-treatment: 1.06 cm³; 0–2 years: 1.61 cm³; 2–4 years: 0.93 cm³; 4–6 years: 0.82 cm³; 6–8 years: 0.82 cm³; 8–10 years: 0.73 cm³; 10–12 years: 0.81 cm³), $p = 0.001$. The same applied for ETV ($p = 0.001$).

Discussion

The main findings of our study are that a 12-year follow-up analysis showed a significant decrease in TTV and ETV only on FSRT-treated patients and that clinical NRs had significantly greater TTV and ETV over time when compared to Rs.

During the last decade, patients with VS were increasingly treated with GK or FSRT versus open-surgical techniques [27]. For these patients, early clinical outcome (facial and trigeminal function, hearing preservation, complication rates and quality of life) has been shown to be at least equal or superior when compared to open surgery. Relative to post-surgical imaging in VS, follow-up imaging of patients who underwent GK or FSRT can be much more challenging due to the typical delayed-responding VS tissue. Therefore, changes in the size of the VS are usually very subtle [9, 12]. In addition, the configuration of the VS often is heterogeneous and conventional mathematical methods are not always sufficient to calculate exact volumes in these tumours [10, 17–19]. Another imaging dilemma after radiation therapy is the phenomenon of transient tumour enlargement followed by subsequent tumour shrinkage, which is frequently observed and has been attributed to either true neoplastic growth, tumoral oedema or tumour expansion following central radiation-induced necrosis [9, 10, 37–39]. To discriminate real therapy failure from temporary tumour swelling and to illustrate long-term tumour behaviour, a user-friendly, workflow-efficient and accurate measurement method is essential for following up on VS patients.

In previous studies, measurements in VS were both time-consuming (manual delineation of tumour on each MRI section for volumetric assessment) and subjective (visual assessment of enhancement patterns) [10, 37]. The semi-automated 3D measurement tool presented herein has several technical strengths: First, we are now able to easily assess the total tumour volume and enhancing tumour volume of VS, taking about 1 min per MRI study with the radiologist always being able to interact and adjust tumour contours if needed. Second, this technique is reader independent. Its reproducibility of results between different radiological readers and preciseness was shown in our comparative fruit measurements and in previous studies [31, 33, 35]. Moreover, the 3D model of the VS generated by the software may also increase the patient's understanding of the disease and may be used for pre- and post-therapy visualization of the tumour for all three treatment modalities.

As indicated above, a characteristic pattern of VS behaviour after radiation treatment has been described in the literature. We were also able to reproduce this pattern in the homogenous patient population (sporadic VS without genetic predisposition and GK or FSRT as first-line treatment) included in this analysis: First, transient tumour enlargement for VS was shown within 2 years after radiation treatment followed by regression in both the GK and FSRT groups. Furthermore, the number of patients who required microsurgical treatment as second-line therapy was low ($n = 4/162$, 2.5 %), which also confirms earlier results [25, 27, 37, 38].

We observed that tumour shrinkage and loss of enhancing volume was significant only for patients treated with FSRT. This might be due to higher patient numbers ($n = 122$ vs. 40) and/or a longer imaging follow-up period for the FSRT group (median 5.3 years) compared

to the GK group (median 1.7 years). To determine clinical utility of our segmentation method, we defined NRs as patients in whom FSRT or GK failed and who need to undergo surgical resection over time ($n = 4$). An additional seven patients showed radiological (tumour volume at last follow-up MRI was more than double the initial treatment volume; the median follow-up time of NR was 44.5 months with a range of 23.8–98.9 months) and clinical progression (new or progressive symptoms at last follow-up MRI). This resulted in 11 patients being NRs (6.79 %). Since there is no consensus about the definition of progression in VS patients after radiotherapy, this definition was somewhat arbitrary [9, 10, 22, 27]. To determine whether increased size and/or new symptoms may be the result of radiosurgery itself rather than treatment failure remains a problem in the routine clinical management of VS patients. Using our criteria, it was found that NRs showed significantly less tumour shrinkage and decreases in enhancing volumes than Rs, which implies that our 3D measurement technique has clinical value. Moreover, 81.8 % of NR tumours had a median TTV under 1 cm^3 (median 0.61 cm^3), supporting the hypothesis of Kapoor et al. [27] that treatment failure is much more common among patients with smaller tumours. Another hypothesis is that smaller tumours grow faster, which causes them to be detected while small.

Our study has several limitations. Due to the retrospective nature of this study, MRI protocols were not uniform (though clinically sufficient) and imaging was performed on different scanner types. Second, the length of follow-up was markedly below the ideal observational period for VS, especially for the GK group (median 1.7 years). This was aggravated by the fact that the number of follow-up MRI studies between the FSRT and GK groups differed as well. The main reason is that FSRT was standard in our institution for many years. In 2008, VS treatment philosophy shifted since the patients' comfort dramatically improved with GK technology (no headframe/screw implant, less intensive procedure for the neurosurgeon and the patient). Shortly afterwards (in 2011), GK was replaced by CyberKnife therapy. To minimize potential confounding, GEE analysis was used, which correlates within-subject and between-subject variables adjusted for time. Additionally, it might be possible that repeated radiation doses affect tumour shrinkage even more than a single dose. Even in a short post-treatment interval, the FSRT group showed significant volume loss, with a tumour shrinkage between baseline and 2- to 4-year follow-up of a median -0.17 cm^3 and a mean -0.92 cm^3 , $p = 0.015$ (GK: median -0.00 cm^3 and mean -0.01 cm^3 , $p = 1.000$). Additionally, FSRT patients started with a smaller median tumour volume (0.96 cm^3) compared to GK patients (1.03 cm^3). A study by Meijer et al. [10] showed greater mean tumour volume reduction in patients treated with single-fraction irradiation compared to patients with fractionated schedule, but this difference was not statistically significant, which might be due to lower patients numbers (single-fraction: $n = 14$; fractionated schedule: $n = 31$) or different techniques used to delineate the tumour.

Furthermore, imaging parameters have to be correlated with clinical data. In another study by Meijer et al. [40], no significant differences were shown in functional outcome (local control, facial nerve and hearing preservation) in patients treated with single-fraction radiosurgery and fractionated radiotherapy. A difference in favour of FSRT was only demonstrated for trigeminal nerve preservation rate [40]. Another study by Andrews et al.

[13] found a significantly higher rate of hearing preservation among FSRT patients, but the median audiometric follow-up only was 38–41 weeks in this study. Combs et al. [41] demonstrated no significant differences in hearing preservation and cranial nerve toxicity between FSRT and single-fraction radiosurgery with a lower dose (13 Gy).

In conclusion, this study shows that our semi-automated 3D measurement technique allows reliable assessment of total tumour size of VS and enhancing tumour volume at baseline and follow-up imaging. Significant tumour shrinkage in a 12-year follow-up was shown for FSRT-treated patients only. Clinical and radiological NRs were found to have greater total tumour volume and enhancing volume than Rs, which supports the validity of this new method. Our findings should be confirmed in larger patient cohorts with longer follow-up MRIs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The scientific guarantor of this publication is David Mark Yousem.

The authors of this manuscript declare relationships with the following companies: JC, grant support: Rolf W. Günther Foundation for Radiological Sciences; ML, Philips employee, grant support: NIH; JFG, consultant: Miocompatibles/BTG, Bayer HealthCare, Guerbet, Nodion/BTG, Philips HealthCare and Jennerex. Grant support: Biocompatibles/BTG, Bayer HealthCare, Philips Medical, Nodion/BTG, Threshold, Guerbet, DOD, NCI-ECOG and NIH-RO1; DR, Salisbury Family foundation; IJT, Nicholl Family Foundation; DMY, Royalties, Oakstone Publishing, LLC Author with royalties, Reed Elsevier Research Grant, Medicolegal Consulting, ACR Educational Center.

The authors state that this work has not received any funding. Carol B. Thompson, Bloomberg School of Public Health kindly provided statistical advice for this manuscript.

Abbreviations

ETV	Enhancing tumour volume
FSRT	Fractionated stereotactic radiotherapy
GK	Gamma Knife
NR	Non-responder
R	Responder
TTV	Total tumour volume
VS	Vestibular schwannoma

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Key Points

- Only FSRT not GK-treated patients showed significant tumour shrinkage over time.
- Clinical non-responders showed significantly less tumour shrinkage when compared to responders.
- 3D volumetric assessment of vestibular schwannoma shows advantages over unidimensional techniques.

Fig. 1.

Flow-chart summarizing patient selection in the study. As first-line therapy, 620/1513 (41.0 %) patients underwent open surgery, 531/1513 (35.1 %) had expectant management ('watch, wait and rescan') and 360/1513 (23.8 %) were treated with radiotherapy. Of 360 vestibular schwannoma (VS) patients who received radiotherapy, those with neurofibromatosis type 2 (NF2) ($n = 79$) and incomplete or poor quality MRI studies (motion artefacts or no administration of contrast media, $n = 85$) were excluded. In addition, patients treated with CyberKnife therapy ($n = 34$) were not included in this study due to its late introduction in

2012 and the resulting short follow-up period until December 2013. At least one pre-treatment study and one retrievable follow-up study were required. In total, 162 patients met the inclusion criteria

Fig. 2.

Left-sided vestibular schwannoma (VS) (**a**), analysis of total tumour volume (TTV) using a 3D segmentation mask (**b** and **c**) and evaluation of enhancing tumour volume (ETV) by placing a region of interest (ROI) in the hypo-enhancing pons (**d**). The colour spectrum shows different areas of enhancement, with red representing the maximum enhancement as described in the text

Fig. 3. Total tumour volume (TTV) (a) and enhancing tumour volume (ETV) (b) changes in Gamma Knife (GK) patients across different time points (pre-GK treatment, 0–2 years, 2–4 years and 4–6 years after GK). Outliers are not shown

Fig. 4.

Total tumour volume (TTV) (a) and enhancing tumour volume (ETV) (b) changes in patients treated with fractionated stereotactic radiotherapy (FSRT) over time (baseline imaging, 0–2 years, 2–4 years, 4–6 years, 6–8 years and 8–10 years after treatment with FSRT). Outliers are not shown

Fig. 5.

Long-term follow-up imaging and 3D segmentation of a 56-year-old (at diagnosis) male patient. For each time point (columns), semi-automated tumour segmentation (first row), a 3D segmentation mask rendering (second row) and quantitative enhancement (third row) are shown. Maximum contrast enhancement of the vestibular schwannoma (VS) was demonstrated pre-therapy (red) with a continuous decrease 2–4 years after radiation treatment (blue). The detailed technique is described in the Materials and methods section

Table 1**Baseline patient characteristics and radiation therapy details**

	SRS (<i>n</i> = 40)	FSRT (<i>n</i> = 122)
Patient characteristics		
• Female/male	22/18	57/65
• Median age in years (range, SD)	62.5 (39–85, 12.3)	56 (30–88, 10.6)
Time between diagnosis of VS and treatment		
• Median, months (range, SD)	10.5 (0–153, 26.2)	5 (1–173, 25.8)
Lesion side		
• Right	19 (47.5 %)	65 (53.3 %)
• Left	21 (52.5 %)	57 (46.7 %)
Lesion type		
• Homogeneous	34 (85.0 %)	95 (77.9 %)
• Heterogeneous with cystic components	6 (15.0 %)	27 (22.1 %)
Indication for radiation treatment (no. of patients)		
• Increase in tumor size	16 (40.0 %)	48 (39.3 %)
• Progressive symptoms	36 (90.0 %)	108 (88.5 %)
• Both	13 (32.5 %)	34 (27.9 %)
VS characteristics before treatment		
• Median TTV in cm ³ (range, SD)	1.03 (0.17–8.52, 1.78)	0.96 (0.11–23.48, 4.28)
• Median ETV in cm ³ (range, SD)	1.00 (0.07–8.33, 1.72)	0.85 (0.06–21.80, 3.80)
Treatment details		
• Median no. of fractions (range, SD)	1	5 (3–30, 3.8)
• Median delivered dose per fraction in cGy (range, SD)	1200 (1200–1400)	500 (130–600, 75.4)
• Median total delivered dose in cGy (range, SD)	1200 (1200–1400)	2500 (1800–5400, 426.0)
Follow-up		
• Median follow-up time, years (range, SD)	1.7 (0.4–8.4, 1.87)	5.3 (0.5–12.0, 2.86)
• No. of retrievable MRIs		
Pre-treatment	40	122
+0–2 years	37	80
+2–4 years	18	72
+4–6 years	7	53
+6–8 years	2	41
+8–10 years	1	19
+10–12 years	0	9
Total	105	396
• No. of NRs	3 (7.5 %)	8 (6.6 %)

SD standard deviation, *VS* vestibular schwannoma, *MRI* magnetic resonance image, *NRs* non-responders