

Fractionated vs. single-fraction stereotactic radiotherapy in patients with vestibular schwannoma

Hearing preservation and patients' self-reported outcome based on an established questionnaire

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Received: 28 July 2016 / Accepted: 6 October 2016 / Published online: 1 November 2016
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Abstract

Background Stereotactic radiotherapy (RT) has been established as a valid treatment alternative in patients with vestibular schwannoma (VS). There is ongoing controversy regarding the optimal fractionation. Hearing preservation may be the primary goal for patients with VS, followed by maintenance of quality of life (QoL).

Methods From 2002 to 2015, 184 patients with VS were treated with radiosurgery (RS) or fractionated stereotactic radiotherapy (FSRT). A survey on current symptoms and QoL was conducted between February and June 2016.

Results Median follow-up after RT was 7.5 years (range 0–14.4 years). Mean overall survival (OS) after RT was 31.1 years, with 94 and 87% survival at 5 and 10 years, respectively. Mean progression-free survival (PFS) was 13.3 years, with 5- and 10-year PFS of 92%. Hearing could be preserved in RS patients for a median of 36.3 months (range 2.3–13.7 years). Hearing worsened in 17 (30%) cases. Median hearing preservation for FSRT was 48.7 months (range 0.0–13.8 years); 29 (23%) showed hearing deterioration. The difference in hearing preserva-

tion was not significant between RS and FSRT ($p = 0.3$). A total of 123/162 patients participated in the patient survey (return rate 76%). The results correlate well with the information documented in the patient files for tinnitus and facial and trigeminal nerve toxicity. Significant differences appeared regarding hearing impairment, gait uncertainty, and imbalance.

Conclusion These data confirm that RS and FSRT are comparable in terms of local control for VS. RS should be reserved for smaller lesions, while FSRT can be offered independently of tumor size. Patient self-reported outcome during follow-up is of high value. The established questionnaire could be validated in the independent cohort.

Keywords Survival · Quality of life · Patient self-reported outcome · Questionnaires · Toxicity

Fraktionierte stereotaktische Radiotherapie vs. Radiochirurgie bei Patienten mit Vestibularisschwannom

Erhalt des Hörvermögens und Patientenselbstbericht anhand eines etablierten Fragebogens

Zusammenfassung

Hintergrund Die stereotaktische Radiotherapie (RT) wurde als gültige Behandlungsalternative bei Patienten mit Vestibularisschwannom (VS) etabliert. Diskussionen über die optimale Fraktionierung laufen jedoch. Der Erhalt von Hörvermögen und Lebensqualität (QoL) sind Hauptziele für Patienten.

Methoden Von 2002 bis 2015 wurden 184 VS-Patienten mit Radiochirurgie (RS) oder fraktionierter stereotaktischer Radiotherapie (FSRT) behandelt und aktuelle Nebenwirkungen und QoL zwischen Februar und Juni 2016 bewertet.

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Ergebnisse Das mediane Follow-up nach RT betrug 7,5 Jahre (Spanne 0–14,4 Jahre), das mittlere Gesamtüberleben (OS) nach RT 31,1 Jahre, mit Überlebensraten von 94 und 87% nach 5 und 10 Jahren und das mittlere progressionsfreie Überleben (PFS) 13,3 Jahre, mit einem 5- und 10-Jahres-PFS von 92%. Patienten mit RS behielten ihr Hörvermögen im Median für 36,3 Monate (2,3–13,7 Jahre). In 17 (30%) Fällen verschlechterte sich das Hörvermögen. Der mediane Gehörerhalt für FSRT betrug 48,7 Monate (Spanne 0,0–13,8 Jahre); 29 (23%) Patienten zeigten eine Verschlechterung. Der Unterschied im Erhalt des Hörvermögens war zwischen RS und FSRT nicht signifikant ($p = 0,3$). Insgesamt nahmen 123/162 Patienten an der Umfrage teil (Rücklaufquote 76%). Die Ergebnisse korrelieren gut mit den Informationen aus den Patientenakten für Tinnitus, Fazialis- und Trigemini-Nebenwirkungen. Signifikante Unterschiede gibt es in Bezug auf Hörschädigung, Gangunsicherheit und Gleichgewichtsstörung.

Schlussfolgerung Unsere Daten bestätigen, dass sowohl RS als auch FSRT bezüglich lokaler Kontrolle vergleichbar sind. RS sollte für kleinere Läsionen angewendet werden, während sich FSRT unabhängig von der Tumorgroße eignet. Der Patientenselbstbericht während des Follow-up-Zeitraums ist von hohem Wert. Der etablierte Fragebogen konnte in dieser unabhängigen Kohorte validiert werden.

Schlüsselwörter Überleben · Lebensqualität · Patientenselbstbericht · Fragebögen · Toxizität

Stereotactic radiotherapy (RT) has been established as a valid treatment alternative in patients with vestibular schwannoma (VS). There is ongoing controversy regarding the optimal fractionation: while some authors clearly prefer short treatment times and report data from radiosurgery (RS) approaches, others favor a fractionated regimen on the basis of a radiobiological benefit of fractionation which is associated with a promising risk–benefit profile for smaller and large VS alike.

Hearing preservation may be the primary goal for VS patients, followed by maintenance of quality of life (QoL). In turn, QoL is influenced by the typical side effects of impaired facial and trigeminal nerve function, tinnitus, imbalance, dizziness, and gait uncertainty. Current treatment options are wait-and-see, microsurgery, RS, and fractionated stereotactic radiotherapy (FSRT), all equally effective depending on the size and location of the tumor [1, 2].

Often the treatment decision depends on the physician's experience and patients' preferences. For large tumors, surgical resection is often preferred, with preservation of facial nerve function in about 85% of cases, while the rate of hearing preservation is about 50% [3–5]. Better outcome and QoL are associated with smaller tumor size.

For small and medium-sized VS, all strategies are possible, with comparable control rates. While surgery is possible, it bears more risks than noninvasive RS or FSRT. For smaller tumors, preservation rates of 90% for facial nerve function and of 80% for hearing can be achieved [6–8].

Recent studies examine very little data on QoL. However, it has been shown that the physician-reported outcome can vary substantially from the patient-reported outcome, and this information should therefore be taken into account when comparing treatment modalities. Particularly for patients with long-term survival, the patient-reported outcome is of high value for treatment evaluation. In the past, the authors of the current paper developed a questionnaire addressing patient-reported outcome. In the present work, the authors sought to validate the questionnaire previously developed by Combs et al. in 2013 [9] in an independent cohort of VS patients, and differentially report on outcome and hearing preservation after single-fraction or fractionated stereotactic radiotherapy (FSRT).

Patients and methods

Patients

From 2002 to 2015, 184 patients with VS were consecutively treated at the Department of Radiation Oncology at the Klinikum rechts der Isar, Munich, Germany. Patient data were collected prospectively in the institutional database directly after therapy or follow-up appointment in a standardized form. The cutoff date for data collection was June 2016. The local ethics committee of the Medical Faculty of the Technische Universität München (TUM) approved the study with vote number 257/16S. Primary endpoints were local control and facial and trigeminal neuropathy, as well as QoL and patient-reported outcome.

Of all patients, 43% were male (80/184) and 57% (104/184) female. Median age at treatment was 60 years (range 16–85 years). The Gardner–Robertson Scale was used to determine hearing status before and after RT; the House–Brackmann Facial Weakness Scale for the facial nerve status.

Of all patients, 8 had received previous surgery within 6 months before RT. Of these, 4 patients suffered from neurofibromatosis type 2 (NF2). The remaining 3 patients with NF2 had undergone surgery more than 4.5 years before RT.

Radiotherapy

In 56 patients, RT was performed as RS with a median dose of 12 Gy. In the remaining 128 patients, RT was performed as FSRT with a median dose of 54 Gy and a median single

Table 1 Patient characteristics

	All	RS	FSRT
Number of patients	184	56	128
Gender (no. of patients)			
Female	104	33	71
Male	80	23	57
Age (years)			
Median	60	63	59
Range	16–85	16–85	17–82
Tumor location			
Right	89	27	62
Left	88	28	60
Bilateral	7	1	6
Intracanalicular	182	56	126
Extracanalicular	156	42	114
Previous surgery (max 6 months before RT)	8	0	8
Neurofibromatosis type 2	7	0	7
PTV volume (ml)			
Median	1.96	1.03	3.55
Range	0.09–41.1	0.09–5.36	0.1–41.1
RT (Gy)			
Median total dose	–	12	54
Range total dose	–	12–20	25–56
Median single dose	–	–	1.8
Range single dose	–	–	1.8–5.0

RS radiosurgery, FSRT fractionated stereotactic radiotherapy, RT radiotherapy, PTV planning target volume

dose of 1.8 Gy. Dose was applied with a Varian Trilogy linear accelerator (LINAC; Varian, Palo Alto, CA, USA). Treatment planning for RS and FSRT was performed using a stereotactic treatment setup with a thermoplastic mask system (Brainlab, Feldkirchen, Germany) and daily image-guided RT (IGRT) by robotic ExacTrac positioning (Brainlab). On contrast-enhanced T1-weighted MRI imaging, the gross tumor volume (GTV) was defined. The planning target volume (PTV) resulted from the GTV with an additional margin of 1–2 mm. The dose was described on the 80% isodose for RS and on the 95% isodose for FSRT. Median PTV volume was 1.96 ml (range 0.09–41.1 ml). For patient characteristics, see Table 1.

Follow-up

Patients were enrolled into a follow-up regimen with assessment 6 months after RT and yearly thereafter, including contrast-enhanced MRI as well as clinical assessment. Additional examinations were scheduled if clinically needed. All decisions regarding further treatments were made on an interdisciplinary basis.

Patient survey

The survey was conducted between February and June 2016. The questionnaire developed by Combs et al. in 2013 [9] was sent to 162 of all 184 patients. Patients living outside Germany and already deceased patients were not included. The survey on patient self-reported outcome focuses mainly on the following aspects: questions regarding symptoms, items assessing overall hearing and QoL before and after RT treatment, post-RT treatments, and status of last (external) follow-up.

Statistics

Statistical calculations were performed using SPSS Statistics v. 23 (IBM, Armonk, NY, USA). For all patients, overall survival (OS) was calculated from the last day of RT until death or last follow-up; progression-free survival (PFS) from the last day of RT until the date of progression or death or last follow-up. Survival analyses were based on the Kaplan–Meier method; PFS and hearing preservation were calculated with the Cox regression method. For univariate analyses of different patient groups, the log-rank test was used. Frequency distributions in the RT groups were tested with the chi-squared test. Comparison of patient-reported side effects with documented information in the patient file was performed using the McNemar test for related samples. A p -value ≤ 0.05 was considered statistically significant.

Results

Outcome

Median follow-up after RT was 7.5 years (range 0–14.4 years, including foreign patients who were lost to follow-up). During the period of analysis, 17 patients died and 12 developed a local recurrence. Mean OS after RT was 13.1 years, with 94 and 87% survival at 5 and 10 years, respectively. For PFS, the mean was 13.3 years; with 5 and 10 year PFS of 92%. Neither OS nor PFS differed significantly between the RS and FSRT groups (OS: $p = 0.9$, PFS: $p = 0.3$; hazard ratio, HR = 2.11; confidence interval, CI = 0.46–9.64; Fig. 1).

Hearing preservation and tinnitus

For the RS group, 19 (34%) patients had useful hearing (grade I/II) before RT, see Table 2. Hearing could be preserved for a median of 36.3 months (range 2.3–13.7 years). Hearing worsened in 17 (30%) cases. Median hearing preservation in the FSRT group was 48.7 months (range

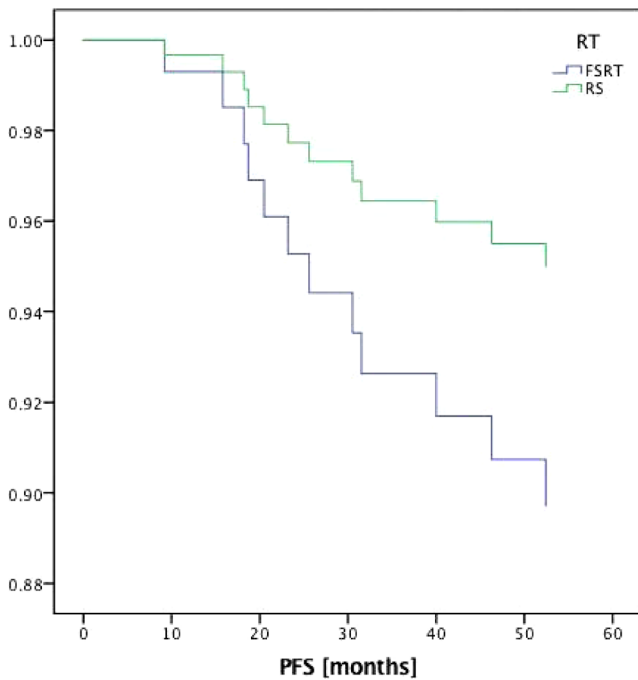


Fig. 1 Progression free survival (PFS) in all patients ($n = 184$), $p = 0.3$. RT radiotherapy, RS radiosurgery, FSRT fractionated stereotactic radiotherapy

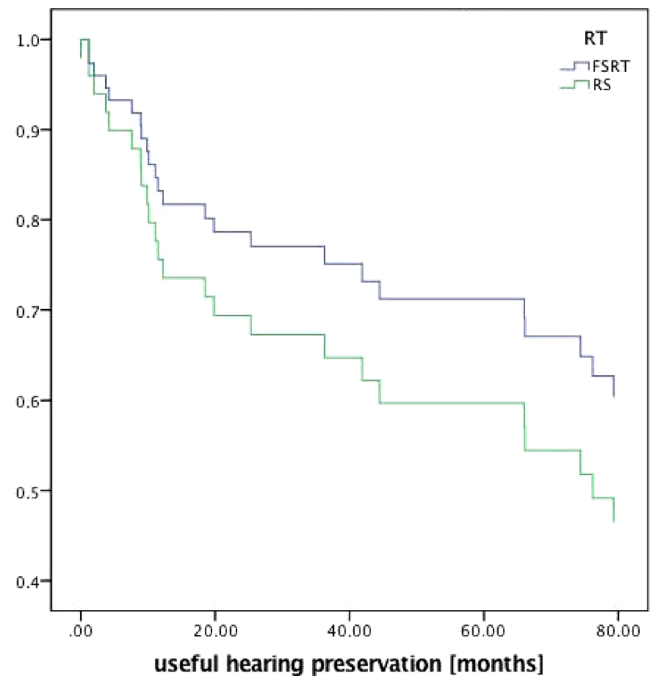


Fig. 3 Useful hearing preservation in patients with initial Gardner–Robertson Scale I and II for both radiotherapy (RT) methods ($n = 65$), $p = 0.3$. RS radiosurgery, FSRT fractionated stereotactic radiotherapy

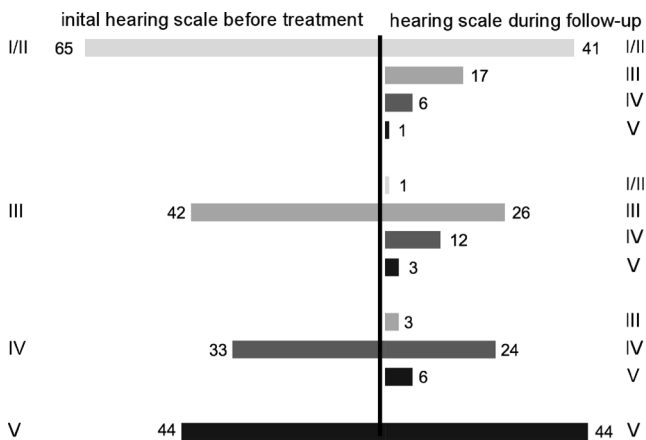


Fig. 2 Development of hearing impairment according to the Gardner–Robertson Hearing Scale during follow-up of each patient; light grey: grade 1/2 (I/II), medium grey: grade 3 (III), dark grey: grade 4 (IV), black grade: grade 5 (V)

0.0–13.8 years). Of all FSRT patients, 29 (23%) showed a hearing deterioration. Development of hearing impairment during the follow-up period of each patient is shown in Fig. 2. For all patients with useful hearing ($n = 65$) before RT, the differences in hearing preservation were not significant (Fig. 3; $p = 0.3$, HR = 0.66, CI = 0.29–1.50) between RS and FSRT. Out of 59 patients without tinnitus, 15 reported post-RT symptoms (8.5%).

Facial and trigeminal nerve toxicity

Of all patients without facial nerve toxicity, 5 developed new symptoms after RT. Facial nerve function could be preserved in 93.5% of all patients. Trigeminal nerve function remained without interference for 89.7%. The distribution was not significantly different between the RS and FSRT groups (facial nerve $p = 0.5$, trigeminal nerve $p = 0.1$).

Dizziness, imbalance, gait uncertainty

Documentation accuracy of dizziness, imbalance, and gait uncertainty was poor, since it is hard for patients and even doctors to distinguish between the three. Rates of new occurrences were recorded between 14 and 20% after RT; however, symptoms improved in most cases during long-term follow-up. Differences between RS and FSRT were not significant for gait uncertainty ($p = 0.5$), dizziness ($p = 0.2$), or imbalance ($p = 0.4$).

Quality of life questionnaire

A total of 123 out of 162 patients participated in the survey, which represents a return rate of 76%. Median follow-up of this subgroup was 9.6 years (1.8 months–14.3 years). The results of the self-reported typical side effects are listed in Fig. 4. Considering the responses of 76% of patients, the results correlate well with the information documented in the

Table 2 Hearing preservation according to the Gardner–Robertson Hearing Scale; facial nerve paresis according to the House–Brackmann Facial Weakness Score; tinnitus, gait uncertainty, vertigo, and imbalance before and after RT

No. of patients (%)	Before RT			After RT		
	All	RS	FSRT	All	RS	FSRT
Gardner–Robertson Hearing Scale						
Grade I	13 (7)	2 (4)	11 (9)	5 (3)	0 (0)	5 (4)
Grade II	52 (28)	17 (30)	35 (27)	37 (20)	10 (18)	27 (21)
Grade III	42 (23)	13 (23)	29 (23)	46 (25)	17 (30)	29 (23)
Grade IV	33 (18)	13 (23)	20 (17)	42 (23)	15 (27)	27 (21)
Grade V	44 (24)	11 (20)	33 (26)	54 (29)	14 (25)	40 (31)
No useful hearing (grades III–V)	119 (65)	–	–	142 (77)	–	–
Facial nerve toxicity (House–Brackmann)						
Grade I	28 (15)	9 (16)	19 (15)	27 (15)	10 (18)	17 (13)
Grade II	15 (8)	3 (5)	12 (9)	9 (5)	1 (2)	8 (6)
Grade III	5 (3)	2 (4)	3 (2)	12 (7)	3 (5)	9 (7)
Grade IV	9 (5)	1 (2)	8 (6)	14 (8)	2 (4)	12 (9)
Grade V	2 (1)	–	2 (2)	2 (1)	–	2 (2)
Grade VI	2 (1)	–	2 (2)	2 (1)	–	2 (2)
Grades II–VI	33 (18)	–	–	39 (21)	–	–
Trigeminal nerve toxicity	23 (13)	6 (11)	17 (13)	34 (18)	9 (16)	25 (20)
Tinnitus	125 (68)	37 (66)	88 (69)	140 (76)	39 (70)	101 (79)
Gait uncertainty	32 (17)	10 (18)	22 (17)	48 (26)	14 (25)	34 (27)
Dizziness	112 (61)	38 (68)	74 (58)	131 (71)	39 (70)	92 (72)
Imbalance	59 (32)	11 (20)	48 (38)	70 (38)	17 (30)	53 (41)

RS radiosurgery, FSRT fractionated stereotactic radiotherapy, RT radiotherapy

Table 3 Comparison of patient-reported side effects and documented information in the patient file

	Patient file (%)	Survey (%)	<i>p</i> -value
Tinnitus before RT	71.3	71.3	1.0
Tinnitus after RT	81.8	76.0	0.296
Facial nerve toxicity before RT	19.5	17.1	0.607
Facial nerve toxicity after RT	17.9	20.3	0.629
Trigeminal nerve toxicity before RT	13.3	18.3	0.286
Trigeminal nerve toxicity after RT	17.5	20.0	0.690
Gait uncertainty before RT	17.4	43.8	0.000*
Gait uncertainty after RT	27.1	46.6	0.001*
Imbalance before RT	36.4	77.1	0.000*
Imbalance after RT	45.0	70.0	0.000*
Hearing impairment before RT	66.7	74.8	0.031*
Hearing impairment after RT	77.2	69.9	0.108

RT radiotherapy

*Significant *p*-values

patient files for tinnitus, facial nerve toxicity (grade II–VI), and trigeminal nerve toxicity before and after RT (Table 3). Significant differences between patient-reported side effects and documented information in the patient file appeared regarding hearing impairment (only before RT), gait uncertainty, and imbalance.

As self-assessed by the patients, side effects improved after RT in 32% (Fig. 5a). The improvement differed between the two RT methods and was significantly better for patients treated with RS compared to FSRT ($p = 0.03$). This result corresponds with the answers to the survey questions “How do you feel after RT?” and “How is your quality of life after RT” (Fig. 5b, c), with 27 and 30% also reporting an improvement in these items, respectively. Overall, QoL was unchanged or improved for about 80% of patients (Fig. 5c), and no significant differences could be observed between the RS and FSRT groups ($p = 0.8$). Of the 17% reporting a reduction in QoL, a total or severe hearing impairment was most often mentioned; three cases were related to secondary illnesses, i. e., stroke, leukemia, and age-related macular degeneration (AMD).

Fig. 4 Self-reported side effects of patients ($n = 123$) before and after radiotherapy (RT)

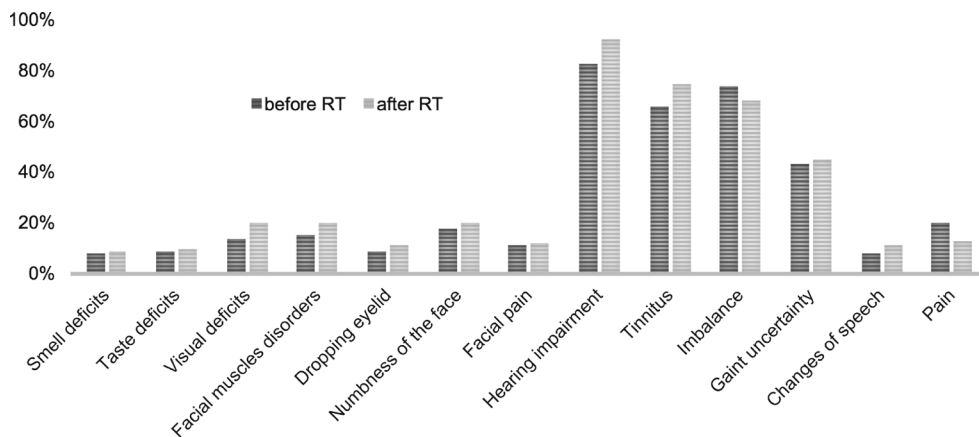
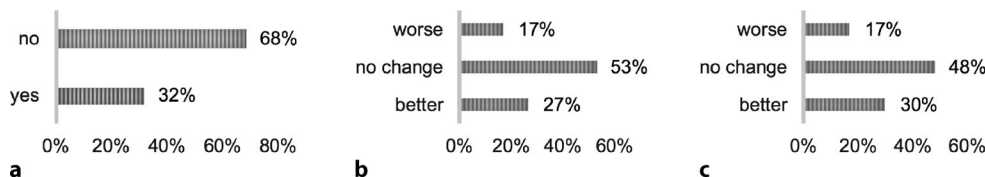


Fig. 5 Diagram showing answers for the question **a** “Did your side effects improve after RT?”, **b** “How do you feel after RT”, **c** “How is your quality of life after RT”. RT radiotherapy



Discussion

Long-term follow-up confirms that both FSRT and RS remain safe and effective in terms of local control and cranial nerve toxicity. Besides objective clinical follow-up, patient-reported outcome underlines the overall beneficial treatment of VS with noninvasive high-precision RT. The questionnaire developed by Combs et al. [9] was validated in this present project in an independent patient population and reveals comparative results. This supports the value of the present questionnaire during follow-up in addition to standard clinical and imaging examination.

For VS, treatment decision-making depends on the size of the lesion as well the clinical presentation of patients. For small and asymptomatic tumors, a wait-and-scan strategy might be followed; generally, average growth ranges between 1 and 3 mm per year, and close clinical and radiological follow-up will be able to capture early recurrence, enabling safe and effective treatment at such a time. Considering hearing development throughout the clinical course, natural hearing deterioration is also present independently of VS, particularly in the aging population. With VS, natural hearing impairment without any treatment is reported to be 56% [10].

Surgery has been the mainstay of treatment over the years. Different anatomical approaches are possible, from translabyrinthine to subtemporal, each associated with specific risk–benefit profiles. Large series of VS report a local control rate of about 90% [11, 12], with a rate of hearing impairment of around 60% [6, 12, 13]. Hearing deterioration generally occurs directly after surgery, whereas any hearing impairment after RT develops over time, in most

cases within the first 6 months when directly attributable to RT.

RT has become established as a noninvasive and toxicity-minimized treatment alternative. Depending on the volume of the lesion, either single-fraction RS or fractionated regimens [14] are possible. Several reports from single institutions have confirmed excellent long-term local control of over 95%, even after 10 and 20 years [15]. Hearing deterioration depends on the series and is between 85 and 90% after 10 and 20 years [16], although RT rarely leads to complete loss of hearing when performed early. For smaller volumes, RS is comparable to fractionated treatment [14]. Smaller series have reported that fractionated treatment might be safer in terms of cranial nerve toxicity, and this certainly may hold true for larger lesions; only recently, Fong and colleagues reported that hearing preservation was higher after fractionated regimens [8]. In a previously published multicenter analysis, the authors of the current study demonstrated comparable hearing preservation for smaller lesions; however, larger lesions were all treated with fractionated concepts, independent of the treating center [14]. To date, there are no clear data regarding which volume can be considered “large”. Prospective and clearly stratified studies are required to define the border between smaller and large lesions, and thus define the threshold for RS vs. fractionated RT. Independent of size, dose is also a strong prognostic factor: it has been shown in the past that single doses exceeding 13 Gy lead to a significant risk of hearing impairment and facial or trigeminal nerve toxicity [17, 18]. For fractionated regimens, no difference in toxicity profiles between 54 and 57.6 Gy has been reported; however, in the study by Champ et al., even more

beneficial toxicity profiles were reported with 46.8 Gy in single fractions [19]. Long-term analysis must confirm that this safety does not compromise long-term local control.

Considering the effectiveness of neurosurgical resection in an experienced team, as well as the beneficial toxicity profile of RT, a combined treatment approach might be the treatment of choice in the future, particularly for larger and brainstem-compressing lesions. Planned partial and maximal safe resection can then be consolidated with highly precise RT to any tumor remnants.

As the validation of the questionnaire by Combs et al. [9] showed reliable results, this is now being implemented in the authors' daily clinical routine. Patient-reported outcome is a valuable addition to standard clinical treatment documentation and leads to improved accuracy and completeness of follow-up data. Furthermore, patients feel better understood and actively included in management of their disease. Particularly in cases where long-term side effects of treatment are relevant and patients are easily lost to follow-up, regularly performed assessment of patient-reported outcome is a suitable tool to quantify symptomatic improvement or worsening. In addition, the collected data can be used to gain further scientific findings. However, it must be considered that the need for continuous validation of QoL questionnaires is substantial, as controllability is a crucial part of the scientific process and data of nonvalidated questionnaires do not match the criteria of good scientific practice.

Conclusion

These data confirm that RS and FSRT are comparable in terms of local control for VS. RS should be reserved for smaller lesions, while FSRT can be offered independently of tumor size. Particularly for larger volumes, a combined treatment approach comprising neurosurgery and RT might be the treatment of choice in the future. In addition to standard clinical and imaging examinations, patient self-reported outcome during follow-up is of high value. The established questionnaire could be validated in the present independent cohort and provides valuable data on outcome after RS or FSRT.

Compliance with ethical guidelines

Conflict of interest K.A. Kessel, H. Fischer, M.M.E. Vogel, M. Oechsner, H. Bier, B. Meyer, and S.E. Combs 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 1964 Helsinki declaration and its later amendments or comparable

ethical standards. Informed consent was obtained from all individual participants included in the study.

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