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Long-term tumor control in Koos grade IV vestibular schwannomas without the need for gross-total resection

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OBJECTIVE The modern management of patients with Koos grade IV vestibular schwannomas (VSs) aims at functional preservation and long-term tumor control. Gross-total resection (GTR) leads to optimal tumor control but frequently also results in permanent facial nerve (FN) palsy. Subtotal resection (STR) or near-total resection (NTR) followed by a wait-and-scan protocol and second-line radiation therapy (RT) in case of progressive residuals yields excellent tumor control rates with less permanent morbidity.

METHODS The authors present the results of their prospective cohort of Koos grade IV VS patients who underwent less-than-total resection followed by a wait-and-scan protocol between January 2009 and December 2019 and discuss the latest evidence on this controversial subject. The cohort was followed up with annual clinical and volumetric outcome analyses after standardized MRI.

RESULTS Forty-eight patients were included in the analysis. The mean extent of resection was 87% (median 91%, range 45%–100%), best fitting into the definition of STR rather than NTR. In 2 cases, the proximal portion of the FN at the brainstem could not be reliably identified and monitored during the initial operation, and a second-stage resection was necessary. At 4.4 years after surgery, 81% (39/48) of the tumor residuals regressed or were stable in size. The percentage of regressive tumor residuals increased over time. Nineteen percent (9/48) of the tumor residuals displayed volumetric progression within a mean time of 35 months (median 36 months, range 14–72 months), resulting in a Kaplan-Meier estimate for progression-free survival of 79% after 4 years; higher postoperative volume showed a linear correlation with higher volumetric progression (factor 1.96, 95% CI 1.67–2.30; $p < 0.001$). Thirty-four of the 48 (71%) patients continue to undergo a wait-and-scan protocol. Second-line RT was performed in 14 patients (29%) within a mean time of 25 months (median 23 months, range 5–54 months), 12 (86%) of whom responded with post-RT pseudoprogression, resulting in an overall tumor control rate of 96%. At the 4.4-year follow-up from the initial resection, 92% of the patients had a good facial outcome (House-Brackmann [HB] grade I or II), 6% had a fair facial outcome (HB grade III), and 2% had a poor facial outcome (HB grades IV–VI). So far, there has been no need for salvage surgery after RT.

CONCLUSIONS STR followed by observation and second-line RT in cases of progression leads to good facial outcome and an excellent tumor control rate in the longer term.

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KEYWORDS vestibular schwannoma; Koos grade IV; near-total resection; radiosurgery; adverse effects; facial nerve outcome

The aims of the neuro-oncological management of Koos grade IV vestibular schwannomas (VSs) are long-term tumor control and the restoration/preservation of neurological integrity.[1–4] "Gross-total resection" (GTR) is a frequently used term in the VS literature from the last few decades and indicates a concept of intended complete tumor removal using microsurgery and intraoperative electrophysiological monitoring.[5] Most authors, however, admitted leaving some tumor behind in selected cases (e.g., to avoid anatomical discontinuity of the facial nerve [FN]). Complete tumor removal offers the best chances of tumor control. Even in the best hands, complete tumor removal remains associated with a very high rate of neurological compromise, particularly of the FN.[1,4,6] While

ABBREVIATIONS EOR = extent of resection; FN = facial nerve; FRT = fractionated RT; FSRS = fractionated SRS; GTR = gross-total resection; HB = House-Brackmann; NTR = near-total resection; RT = radiation therapy; SRS = stereotactic radiosurgery; STR = subtotal resection; VS = vestibular schwannoma.

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the unilateral loss of serviceable hearing is generally well tolerated by affected patients,[7–9] a visible and permanent FN palsy (House-Brackmann [HB] grade III or VI) is not, for psychological and functional reasons.[4,6] A visible FN palsy is becoming an unacceptable complication for patients with a benign tumor in the era of intraoperative electrophysiological monitoring, image-guided surgery, and stereotactic radiosurgery (SRS). Ever since, treatment strategies with a greater emphasis on functional integrity have been introduced.[10–13] Concepts with intended less-than-total surgical removal of large VSs have increasingly been practiced to optimize the functional outcome at the cost of leaving a tumor residual that may remain stable or even regress over time.[10,14,15] The definition of resection grades shows a certain degree of variation in the literature. Subtotal resection (STR) was defined by Haque et al. as a > 90% tumor removal,[5,16] while other studies used a 95% threshold,[3,16–19] > 25-mm^2 residual tumor area, or > 2-mm-thick pad of residual tumor on postoperative imaging.[15,16] STR mainly focuses on reducing the mass effect on the brainstem at the cost of larger postoperative tumor residuals.[20,21] Near-total resection (NTR) has been defined as a tumor removal rate of > 95%[3,16–19,22] or if there remains ≤ 25 mm^2 residual tumor area or ≤ 2-mm-thick pad of residual tumor on postoperative imaging.[15,16,23–25] In other studies, NTR indicated a concept aiming at an extensive tumor resection to decrease mass effect on the brainstem by thinning out the tumor capsule as much as possible under electrophysiological monitoring and image-guided surgery but refraining from microsurgical dissection of the FN.[10,26] NTR alone may be superior to STR alone for tumor control.[24] It may be inferior to STR alone in terms of hearing and FN preservation.[27] However, quantitative definitions remain problematic, as relative volume reductions in comparison to the initial total volume have their limitations and a universal outcome reporting of STR and NTR for large VS is still lacking.[16,23] Postoperative tumor residuals may be treated by adjuvant SRS approximately 6 months after surgery as an integral part of the treatment concept[20,27] or conservatively observed using a wait-and-scan protocol and only treated by second-line SRS at the time of progression.[21] Overall, studies addressing postoperative follow-up protocols after STR for VS remain scarce, and the optimal regimen still needs to be found.[21,26] The current study reports an update on tumor control, morbidity, and the need for second-line RT following a wait-and-scan period in patients after an intended less-than-total resection strategy best fitting into the definition of STR rather than NTR.[26]

Methods

All patients with Koos grade IV VSs treated by the first (M.R.) and last two (D.B. and L.M.) authors between January 1, 2009, and December 31, 2019, were enrolled after ethics committee approvals were obtained for retrospective and prospective data collection. Written informed consent was obtained from all patients.[26] This was a single-center retrospective (2009–2016) and prospective (2017–2019) cohort study. No clinical trial registration was required.

Study Population

Newly diagnosed previously untreated VSs meeting the criteria for a Koos grade IV tumor[28] that underwent STR were included in this study. The main analysis was performed on a homogeneous cohort of 48 patients extracted from 58 patients who underwent surgery during the study period. Forty-four of the 46 patients from the original cohort[26] between January 1, 2009, and December 31, 2015, were assessed as a subgroup for consistent time-dependent outcome reporting at 2 and 5 years. A detailed study inclusion profile is provided in Fig. 1.

Operative Technique

A retrosigmoid transmeatal approach in the supine position with the head rotated away from the lesion supported by image guidance (iPlan Cranial, version 3.0, Brainlab AG) by a single team of surgeons was performed in all cases. Neuromonitoring was performed, including electromyography for cranial nerves VI, VII, and IX–XII; brainstem auditory evoked potentials measuring the first wave to detect brainstem or intracranial lesioning of cranial nerve VIII; and motor and somatosensory evoked potentials. Surgery followed standardized steps best fitting into STR to achieve the widest possible resection while preserving FN function under electrophysiological monitoring throughout the operation.[26] A detailed description is provided in Fig. 2.

Data Assessment and Collection

Volumetric analysis was performed on routine MRI sequences (constructive interference in a steady-state and T1-weighted Gd-enhanced sequences) by two independent experts blinded to the operative reports using the iPlan Cranial software tool.[29] Clinical examination was performed by a board-certified neurosurgeon before and after surgery until discharge. Cochlear nerve function was audiometrically evaluated before and after surgery with pure-tone audiograms and speech discrimination testing. Relevant data were entered into an Excel database (version 14.0.7, Microsoft Corp.) securely stored on a password-protected in-house computer.

Follow-Up

Outpatient follow-up was performed by the first (M.R.) and last two (D.B. and L.M.) authors 4–6 weeks after surgery and then once per year. MRI scans were obtained before surgery, within 3 months after surgery, and then once per year.

Study Variables

The following variables were recorded: patient characteristics (age, sex, type of surgery, and shunt dependency), initial tumor characteristics (volume [in cm^3], morphology, and immunohistopathology), tumor residual characteristics (volume [in cm^3], topo-anatomical distribution, and extent of resection [EOR] as a percentage [assessed by an independent reader on Gd-enhanced T1-weighted MRI as first postoperative tumor volume/preoperative tumor volume × 100]), symptoms at presentation and at the first and last follow-ups (serviceable ipsilateral hearing defined as

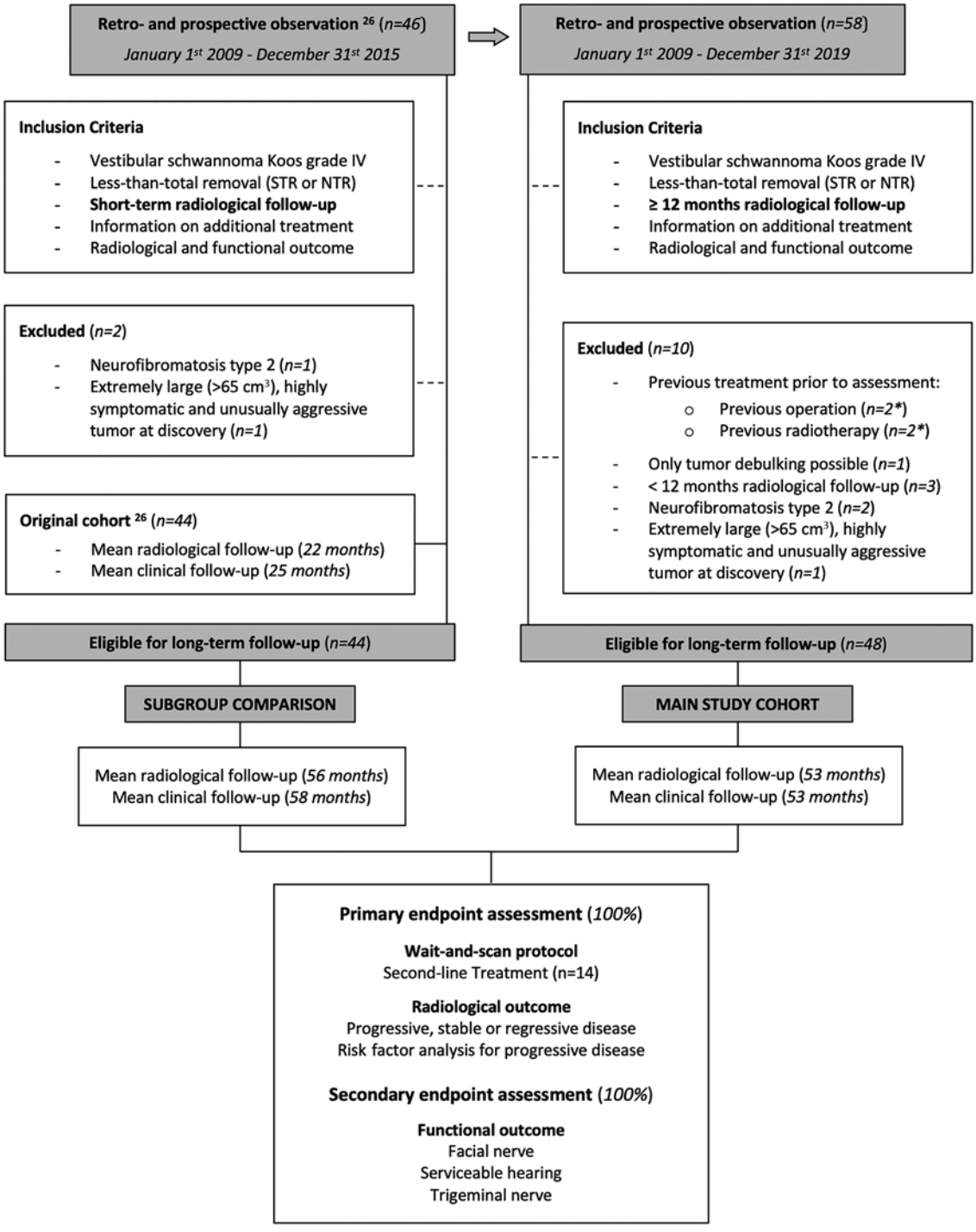

FIG. 1. Patient inclusion profile. Ethics committee approval was obtained for retrospective data collection between January 1, 2009, and December 31, 2015, with 46 patients eligible, and prospective data collection from January 1, 2016, to December 31, 2019, with 12 patients eligible, resulting in 58 patients eligible between January 1, 2009, and December 31, 2019. For final analysis, 8 patients were excluded because of < 12 months of follow-up of the tumor residual, association with neurofibromatosis type 2, or VS recurrence with volumetric progression after previous non-STR surgery or RT. One patient was excluded because the operative procedure was prematurely terminated due to uncontrollable cerebellar swelling and unusually high vascularization and adherence of the tumor in a very short-necked and obese patient so that only partial tumor debulking could be achieved. Another patient was excluded because of an extremely large, highly symptomatic, and unusually aggressive VS (> 65 cm^3 at discovery, annual growth rate > 15 mm in maximal diameter), again not allowing more than tumor debulking to be achieved. *One patient underwent both previous surgery and RT before less-than-total removal.

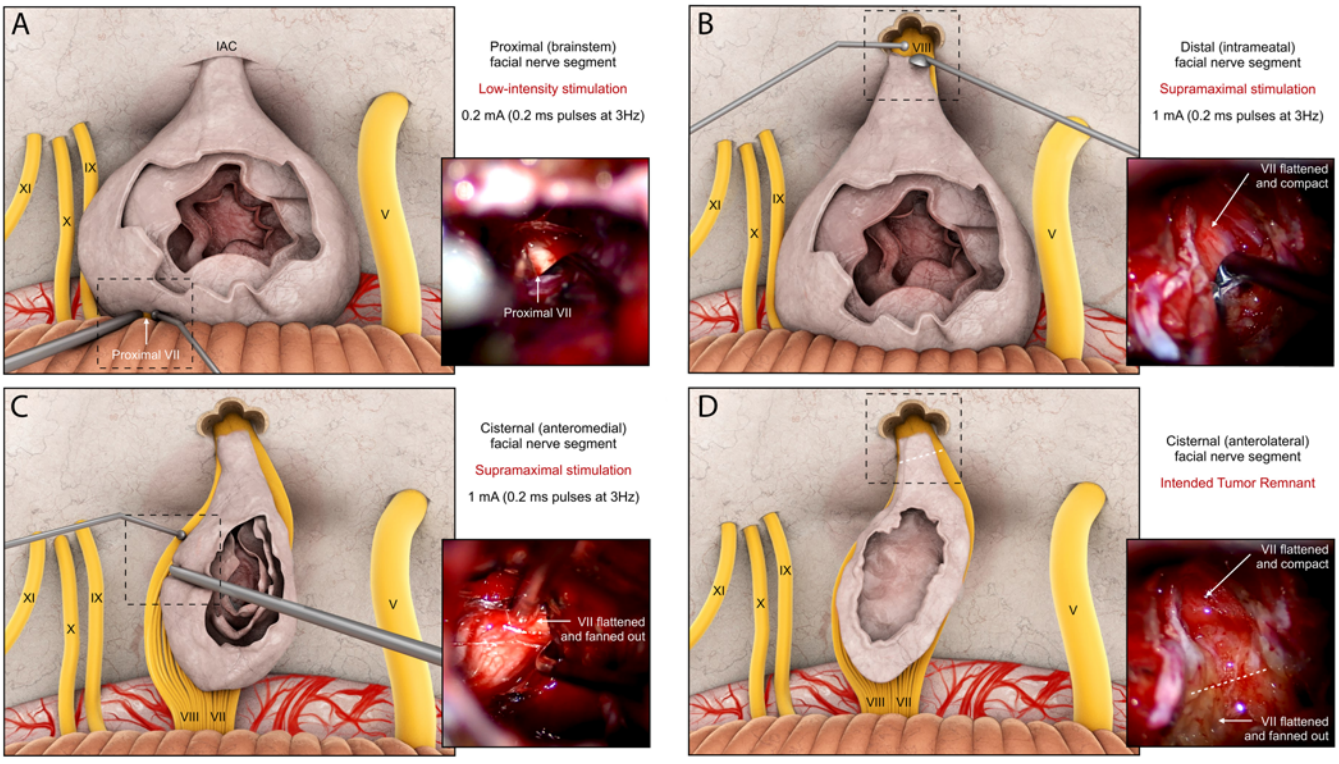

FIG. 2. FN visualization and electrophysiological identification during subtotal resection of a Koos grade IV VS. Artistic rendition paired with intraoperative photographs. After retrosigmoid craniotomy, durotomy, and CSF release, the lateral tumor capsule is exposed and inspected to detect atypical nerve displacement. This inspection is supplemented by electrical stimulation of the tumor surface (e.g., 1 mA) to detect FN branches that might not be visible under the microscope. Stimulation of the spinal accessory nerve (XI) serves as a positive control of the technical intraoperative monitoring setup. The tumor capsule is then entered in the safe lateral zone, and internal decompression is performed in a usual fashion with the assistance of an ultrasonic aspirator and intraoperative navigation. **A:** After adequate intracapsular decompression, the tumor capsule is mobilized, and the FN (VII) is identified at its exit point at the brainstem. Ideally, this spot can be confirmed by electrophysiological stimulation with 0.1–0.2 mA, thus providing an ideal monitoring of the entire FN integrity during the following surgical steps. **B:** The internal auditory canal (IAC) is opened. The distal FN is identified with supramaximal stimulation using 1 mA (0.2-msec pulses at 3 Hz), followed by intrameatal tumor decompression and microsurgical skeletonization of the meatal portion off the FN without relevant adherence as the nerve is usually flattened but compact. **C:** With the proximal and distal ends of the FN having been identified, the trajectory of the FN can now be estimated and the tumor resection continued without dissecting the tumor off of the FN in its cisternal portion, where the nerve usually is flattened, fanned out, and tightly adherent to the tumor capsule. Also, in cases of an apparently favorable tumor-nerve interface, the neurosurgeon refrains from dissecting the FN in every single case. This is the critical difference between the study's concept of intended STR and GTR, where skeletonization of the nerve along the tumor capsule is an integral part of the procedure. **D:** The iterative use of electrostimulation at the brainstem, in the meatus, and along the cisternal tumor capsule allows us to increasingly understand the actual trajectory and localization of the FN; this information in turn helps to optimize further thinning of the tumor capsule. The anterolateral tumor capsule is left along the vulnerable cisternal portion of the FN before entering the internal auditory canal (*dotted white line*), where the nerve is invariably flattened and fanned out, and on the proximal (brainstem) side of the nerve, where a thicker tumor layer can be left in place adjacent to the cisternal portion of the nerve in some cases. V = trigeminal nerve; VIII = vestibulocochlear nerve; IX = glossopharyngeal nerve; X = vagus nerve. © Michel Roethlisberger, published with permission.

Gardner-Robertson class 1 or 2[9] or the American Medical Association Council on Physical Therapy loss ≤ 50 dB;[30] FN function assessed by the HB scale, stratified into good [HB grade I or II], fair [HB grade III], and poor [HB grades IV–VI] groups;[31] and function of the other cranial nerves), and information on additional treatment modalities (reoperation and/or second-line radiation therapy [RT] including SRS, fractionated SRS [FSRS], or fractionated RT [FRT]).

Endpoint Assessment

The primary endpoint of the study was the radiological finding of disease progression at the last follow-up, defined as a volume increase by at least 25% compared with the residual volume at the first follow-up. Stable disease was defined as change in tumor mass (i.e., increase as well as decrease) of < 25%. Disease regression was defined as a volume decrease by at least 25%.[26,32,33] The secondary endpoints were second-line treatment modalities, response rates, and functional outcomes at the last follow-up.[32,33]

Statistical Considerations

Statistical analysis and data illustration were performed using R statistical software (The R Foundation for Statisti-

cal Computing) in RStudio (version 3.4.2, posit.co). Numbers and percentages are provided for categorical data and medians for continuous data. Since follow-up times varied widely across patients, the volume measurement closest to the median follow-up time was considered most suitable for patient-to-patient comparisons. To investigate the predictive power of baseline characteristics as well as the postoperative volume, a multiple linear regression model with log-transformed volume measurements as response was used. To account for the repeated measurements of volumes, random effects were included for the patients, and the longitudinal model estimated by a generalized estimating equations approach was built to obtain estimates with their 95% CIs.

Missing Values

Our study had a 100% follow-up rate for the primary and secondary endpoint assessments. Data are reported according to the STROBE guidelines for observational studies.[34]

Results

Fifty-eight consecutive patients underwent surgery for a Koos grade IV VS. From this continuation of the earlier series,[26] 48 patients were amenable for the final analysis (Fig. 1).

Baseline Characteristics

The mean patient age was 57 years (median 56 years, range 23–87 years). Ninety-eight percent of patients presented with good FN function (HB grade I or II). Serviceable hearing was confirmed in all patients on the opposite side. After STR, the initial radiological follow-up was performed at a mean of 3 months (median 2 months, range 0.1–16 months). The tumor residuals were mainly located in the cisternal segment or the porus acusticus (34/48, 71%). The mean EOR was 87% (median 91%, range 45%–100%) (Table 1, Supplemental Table 1).

Overall Follow-Up

The mean overall last radiological outcome assessment time point (48, 100%) was 52 months (median 49 months, range 12–111 months). The mean overall last clinical outcome assessment time point was 53 months (median 51 months, range 12–126 months). For the postsurgical cohort still undergoing a wait-and-scan protocol (34, 71%), the mean radiological follow-up time was 47 months (median 47 months, range 12–87 months), and the mean clinical follow-up time was 47 months (median 50 months, range 12–84 months). For the postsurgical cohort that did require any second-line therapy (14, 29%), the mean radiological follow-up time was 66 months (median 70 months, range 24–111 months), and the mean clinical follow-up time was 69 months (median 70 months, range 12–126 months) (Tables 2 and 3).

Outcome After STR

Resection via the retrosigmoid approach offered safe treatment with a low profile of surgical complications. The majority of the tumor residuals (39/48, 81%) either continued to regress or remained stable in size, while 9 of 48 (19%) progressed in size at the last radiological follow-up within a mean time of 35 months (median 36 months, range 14–72 months) (Table 2, Supplemental Table 2). Compared with the 44 patients from the original cohort, 1 additional case of progression was identified within these 3 years of difference.[26] The proportion of regressive tumor residuals nearly doubled between the short-term[26] and the longer-term follow-up (Table 4). The outcome of FN function at the last clinical follow-up was good (HB grade I or II) in 92% of cases, fair (HB grade III) in 6%, and poor (HB grades IV–VI) in 2%. Eleven of 48 (23%) patients had a serviceable hearing on the affected side at the first clinical follow-up (Table 3, Supplemental Tables 3 and 4). When compared with the 44 patients from the original cohort, the good initial outcome of FN function in 89% of patients as well as hearing preservation (6/44, 14%) remained stable over the longer term (Table 4).

Wait-and-Scan Protocol After STR

All 48 patients were initially followed up with regular imaging, 34 of whom (71%) have not undergone second-line treatment up to the present. These patients were generally older with a higher female/male ratio and a somewhat lower tumor volume at baseline. During the wait-and-scan period, 32 of 34 (94%) tumor residuals either continued to regress or remained stable in size, while 2 of 34 (6%) progressed at the last radiological follow-up (Tables 1 and 2).

Second-Line RT After STR

Fourteen of 48 (29%) patients, all of whom showed tumor residual growth during the wait-and-scan period, were referred for second-line RT within a mean time of 25 months after surgery (median 23 months, range 5–54 months). RT consisted of SRS (single-session Gamma Knife radiosurgery with a 12-Gy isodose) in 9 of 14 (64%) patients with a mean target volume of 1348 cm^3 (median 1330 cm^3, range 400–2740 cm^3), FSRS (25-Gy isodose) in 1 of 14 (7%), and FRT (54-Gy isodose) in the remaining 4 of 14 (29%) patients with a mean target volume of 2340 cm^3 (median 1931 cm^3, range 1033–4466 cm^3). The mean preoperative tumor volume was somewhat greater in the group receiving second-line RT, but the residual rate and EOR were nearly identical. At the last radiological follow-up, half of the tumor residuals (7/14 [50%]) were either stable or regressed after second-line RT. The other half of the tumor residuals (7/14 [50%]) demonstrated tumor progression at the last follow-up when compared with the first follow-up (Tables 1 and 2, Supplemental Tables 5 and 6).

Any increase in tumor residual volume after RT with subsequent shrinkage was classified as post-RT pseudoprogression, identified in 12 of 14 (86%) patients. The mean latency of pseudoprogression onset time was 11 months (median 7 months, range 4–36 months), with decreasing volumes after a mean of 21 months (median 16 months, range 5–67 months). The remaining 2 patients (14%) demonstrated a true progression after second-line RT at the last follow-up; however, 1 of these 2 patients died of cardiovascular morbidity and was lost to follow-up (Table 2, Fig. 3). The rate of serviceable hearing was

TABLE 1. Baseline demographics of 48 patients with a Koos grade IV VS undergoing less-than-total resection followed by a wait-and-scan protocol

	Undergoing Wait-&-Scan Protocol at Last FU (34 [71%])	Received 2nd-Line RT at Last FU (14 [29%])	Total Cohort at Last FU (48 [100%])
Patient characteristics			
Sex			
Female	21 (62)	6 (43)	27 (56)
Female/male ratio	1.6	0.8	1.3
Mean age, yrs	60 (61 [23–87])	51 (50 [38–82])	57 (56 [23–87])
Initial surgical treatment			
Retrosigmoid approach	34 (100)	14 (100)	48 (100)
Single-session op*	34 (100)	12 (86)	46 (96)
VP shunt prior to op	3 (9)	1 (7)	4 (8)
Tumor characteristics			
Lt side	18 (53)	8 (57)	26 (54)
Mean preop tumor vol, cm^3	10.0 (7.9 [2.2–27.3])	11.6 (9.6 [2.5–21.7])	10.5 (8.1 [2.2–27.3])
Morphological characteristics			
Cystic	5 (15)	2 (14)	7 (15)
Solid	29 (85)	12 (86)	41 (85)
Histology			
WHO grade I	32 (94)	14 (100)	46 (96)
Atypical/pleomorphic	2 (6)	0 (0)	2 (4)
Proliferative activity			
Ki-67/MIB index <3	6 (18)	2 (14)	8 (17)
Ki-67/MIB index >5 to <10	27 (79)	10 (71)	37 (77)
Ki-67/MIB index >10	1 (3)	2 (14)	3 (6)
Tumor residual characteristics			
Main location of residual†			
Brainstem‡	4 (12)	4 (29)	8 (17)
Cisternal segment or porus‡	25 (74)	9 (64)	34 (71)
Internal acustic meatus‡	3 (9)	1 (7)	4 (8)
No residual visible on Gd-enhanced T1WI§	2 (6)	0 (0)	2 (4)
Mean time to 1st radiological FU, mos	2 (2 [0.1–6])	3 (2 [1.7–15.9])	3 (2 [0.1–16])
Mean postop tumor vol, cm^3	1.4 (0.6 [0.0–8.4])	1.6 (1.1 [0.2–6.3])	1.4 (0.8 [0.0–8.4])
Mean tumor residual rate, %	13 (7.4 [0.00–54.7])	14 (11.8 [3.6–35.4])	13 (9 [0–55])
Mean EOR, %	86 (93 [45.3–100])	86 (88 [64.6–96.4])	87 (91 [45–100])
Symptom(s) at presentation			
General			
Asymptomatic	3 (9)	1 (7)	4 (8)
Headache	3 (9)	0 (0)	3 (6)
Vestibular function			
Ataxia	12 (35)	4 (29)	16 (33)
Imbalance	14 (41)	5 (36)	19 (40)
Vertigo	13 (38)	4 (29)	17 (35)
Ipsilat cochlear function			
Serviceable hearing: AMA-CPT loss ≤50 dB	20 (59)	7 (50)	27 (56)
Hypoakusis: AMA-CPT loss ≤50 dB	9 (26)	5 (36)	14 (29)
Anakusis	12 (35)	4 (29)	16 (33)
Tinnitus	8 (24)	4 (29)	12 (25)
Ocular motility			
Nystagmus	3 (9)	1 (7)	4 (8)
Diplopia	1 (3)	0 (0)	1 (2)

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TABLE 1. Baseline demographics of 48 patients with a Koos grade IV VS undergoing less-than-total resection followed by a wait-and-scan protocol

	Undergoing Wait-&-Scan Protocol at Last FU (34 [71%])	Received 2nd-Line RT at Last FU (14 [29%])	Total Cohort at Last FU (48 [100%])
Symptom(s) at presentation (*continued*)			
Normal function of ipsilat trigeminal nerve	22 (65)	8 (57)	30 (62)
Ipsilat FN			
Good: HB grade I or II	33 (97)	14 (100)	47 (98)
Fair: HB grade III	1 (3)	0 (0)	1 (2)
Lower cranial nerves: dysarthria	1 (3)	0 (0)	1 (2)

AMA-CPT = American Medical Association Council on Physical Therapy; FU = follow-up; T1WI = T1-weighted image; VP = ventriculoperitoneal.
Values are presented as the number of patients (%) or mean (median [range]) unless stated otherwise.
* Two-stage surgery was necessary in 2 cases because of unusual circumstances (see footnote in Table 2).
† Maximal tumor thickness was measured on postoperative axial Gd-enhanced T1-weighted MRI.
‡ These values total more than 100% because some patients had a tumor residual covering more than 1 location.
§ In 2 cases, the tumor residual was so small that it could not be detected on postoperative MRI. However, a microscopic tumor residual was reported along the cisternal part of the FN, and no attempt was made to dissect the tumor capsule off.

somewhat higher among patients who went on to undergo second-line RT (6/14, 42%), 2 (14%) of whom lost serviceable hearing after second-line RT (Table 3, Supplemental Table 3). When compared with the 44 patients from the original cohort,[26] 4 times more patients underwent second-line RT after a mean follow-up period of 56 months. There have been no cases of second-line salvage surgery in the longer-term follow-up so far (Table 4).

In the longitudinal linear model, only the postoperative volume was found to be a statistically significant risk factor for volumetric progression, with a twofold increase in the first postoperative volume correlating with an increase in subsequent volumetric measurements by a factor of 1.96 (95% CI 1.67–2.30). Our study did not provide enough evidence to identify statistically significant predictors for second-line RT after STR (Fig. 4, Supplemental Tables 7 and 8).

The Kaplan-Meier estimate revealed a progression-free survival of 93% after 2 years, 87% after 3 years, and 79% after 4 years. The probability of remaining free of second-line RT was 93% after 1 year, 82% after 2 years, 74% after 3 years, and 68% after 4 years (Fig. 3, Supplemental Table 9).

Discussion

We report our extended experience with a treatment paradigm for Koos grade IV VSs that we have described previously.[26] This paradigm consists of 1) an aggressive microsurgical tumor reduction with the aid of imaging guidance and intraoperative neuromonitoring, without dissection of the tumor capsule off the FN resulting in STR; followed by 2) a wait-and-scan MRI protocol including volumetry; and 3) second-line highly conformal RT in case of secondary progression. The present analysis confirms our short-term results:[26] a mean EOR of 87%, an excellent or good FN function in 92%, and a tumor control rate of 96% after a mean of 4.4 years of postsurgical follow-up.

At the cost of higher morbidity, the traditional GTR concept has the potential advantage of minimizing the burden related to the risk of tumor recurrence and of potential additional treatments.[16,26] Five-year recurrence rates of 1% have been reported after GTR; long-term MRI follow-up is therefore also necessary in these cases.[35] After STR, tumor recurrence has been described in 6.2%–43.6% of the cases depending on the study.[3,15,16,20,21,23,24,36] The reported risk of recurrence may be up to 9 times higher after STR than after NTR or GTR; in case of recurrence, second-line RT has proven safe and very effective in a multitude of studies.[3,15,23,25,27,35] In accordance, we observed volumetric progression in one-fifth of our tumor residuals, all of which occurred within the first few years after surgery.[26] Nevertheless, we achieved a tumor control rate of 96% with the use of second-line RT, in line with current literature findings (median 95%, range 87%–100%).[21]

On the other hand, 92% of our patients had an excellent or good FN function after 5 years, with only 1 case (2%) of persistent complete FN palsy. This rate is in line with the current literature (median 90%, range 55%–100%) and compares favorably with series following GTR.[4,21,37] Our results and the available literature on patients with large VSs indicate that the concept of GTR may no longer be justified. It should rather be abandoned for a strategy of STR, putting high emphasis on functional integrity. The safety and efficacy of such FN-centered surgical regimens combined with second-line SRS, however, remain scarcely documented in the literature, with a high variability concerning EOR, timing of SRS, follow-up intervals, and longevity among centers.[21] There still are relevant questions that need to be answered to optimize these multimodal regimens. As a first step, minimum goals in terms of safety, standardization, and reproducibility of STR need to be defined. One may argue that the surgical technique described in the present study may not be safe enough. Despite avoiding thorough dissection of the tumor capsule from the FN, 4 patients experienced permanent FN palsy. The patient with the worst outcome (HB grade VI) had FN impairment at initial presentation (HB grade III). In this case, our technique probably was too aggressive for an

TABLE 2. Surgical and radiological outcomes of 48 patients with a Koos grade IV VS undergoing less-than-total resection followed by a wait-and-scan protocol

	Undergoing Wait-&-Scan Protocol at Last FU (34 [71%])	Received 2nd-Line RT at Last FU (14 [29%])
2nd-line op		
2-stage op*	0 (0)	2 (14)
Mean time from 1st to 2nd op, mos	—	20 (20 [15 to 26])
CSF leakage necessitating revision & VP shunt placement	0 (0)	1 (7)
Mortality	0 (0)	0 (0)
2nd-line RT		
SRS: Gamma Knife, 12-Gy isodose	—	9 (64)
FSRS: 25-Gy isodose		1 (7)
FRT: 54-Gy isodose	—	4 (29)
Mean time from op to RT, mos	—	25 (23 [5 to 54])
Mean time to last radiological FU, mos	47 (47 [12 to 87])	66 (70 [24 to 111])
Mean tumor vol at last FU, cm^3	0.8 (0.2 [0.0 to 6.8])	2.2 (1.3 [0.2 to 8.5])
Mean absolute vol change from 1st to last FU, cm^3	−0.6 (−0.2 [−4.65 to 2.0])	0.6 (0.1 [−0.85 to 3.2])
Overall volumetric outcome		
Stable or regressive disease (39 [81%])		
Stability at last FU, <25% vol change	8 (24)	3 (21)
Regression at last FU, ≥25% vol decrease	24 (71)	4 (29)
Any temporary vol decrease	8 (24)	5 (36)
Mean onset time, mos	9 (10 [3 to 13])	9 (6 [4 to 12])
Any temporary vol growth	8 (24)	4 (29)
Mean onset time, mos	27 (25 [10 to 52])	24 (20 [17 to 39])
Progressive disease (9 [19%])		
Progression at last FU, ≥25% vol growth	2 (6)	7 (50)
Mean onset time, mos	54 (54 [37 to 72])	29 (34 [14 to 45])
Any temporary vol decrease	1 (3)	5 (36)
Mean onset time, mos	46 (46 [46])	12 (9 [7 to 21])
Any temporary vol growth	0 (0)	6 (43)
Mean onset time, mos	—	34 (43 [14 to 48])
Post-RT pseudoprogression†	—	
Any transient vol decrease following vol growth after RT	—	12 (86)
Mean onset time to pseudoprogression, mos	—	11 (7 [4 to 36])
Mean onset time to vol decrease after pseudoprogression, mos	—	21 (16 [5 to 67])
Post-RT progression‡	—	
Documented vol growth w/o vol decrease after RT	—	2 (14)
Mean onset time to non–post-RT progression after RT, mos	—	25 (25 [22 to 28])

Values are presented as the number of patients (%) or mean (median [range]).

* In 2 cases, the proximal portion of the FN could not be reliably identified and monitored at the brainstem and resection was halted at an early stage. Postoperative MRI revealed a large amount of residual tumor with remaining mass effect; thus, second-look surgery was performed. In the first case, tumor reduction was not possible because of the unusually strong scarring, firm consistency, and high vascularization of the tumor. In the second case, the tumor volume could be safely reduced to 4% of the initial volume.

† Transient progression induced by radiosurgery followed by stabilization or decrease.

‡ One patient died of cardiac comorbidity with a documented progress at the last follow-up. The other patient has a stable but overall progressive tumor residual, where further dynamics remains unclear. A late response with transient progression induced by SRS followed by stabilization or decrease is still possible.

already dysfunctional FN, which may be more vulnerable to indirect manipulation by stretching and compression; the surgical exposure at the brainstem or the meatus most likely resulted in neurapraxia or axonotmesis rather than neurotmesis.[4] In another patient, the course of the FN was atypical, as the nerve was visible along the upper lateral tumor capsule and was therefore well exposed to repetitive mechanical stretching and compression during tumor decompression.[4,26] It is unlikely that any surgical strategy will ever be able to reduce the risk of FN palsy to zero.

TABLE 3. Functional outcomes of 48 patients with a Koos grade IV VS undergoing less-than-total resection followed by a wait-and-scan protocol

	Undergoing Wait-&-Scan Protocol at Last FU (34 [71%])	Received 2nd-Line RT at Last FU (14 [29%])
Mean time to 1st clinical FU, mos	2 (0.5 [0.2–17])	3 (1 [0.2–14])
Symptoms at 1st FU		
Vestibular function		
Imbalance	2 (6)	0 (0)
Vertigo	6 (18)	1 (7)
Cochlear function: serviceable hearing (AMA-CPT loss ≤50 dB)	5 (15)	6 (42)
Ocular motility		
Nystagmus	3 (9)	0 (0)
Diplopia	0 (0)	1 (7)
Trigeminal nerve: normal function	28 (82)	12 (86)
FN		
Good	26 (76)	13 (93)
HB grade I	17 (50)	10 (71)
HB grade II	9 (26)	3 (21)
Fair: HB grade III	3 (9)	1 (7)
Poor	5 (15)	—
HB grade IV	4 (12)	—
HB grade VI	1 (3)	—
Shunt-dependent hydrocephalus, total/new	4/1 (12)	1/0 (7)
Mean time to last clinical FU, mos	47 (50 [12–84])	69 (70 [12–126])
Symptoms at last FU		
Vestibular function		
Ataxia	1 (3)	1 (7)
Imbalance	2 (6)	1 (7)
Cochlear function: serviceable hearing (AMA-CPT loss ≤50 dB)	5 (15)	4 (29)
Tinnitus	0 (0)	1 (7)
Trigeminal nerve: normal function	30 (88)	12 (86)
FN		
Good	31 (91)	13 (93)
HB grade I	20 (59)	12 (86)
HB grade II	11 (32)	1 (7)
Fair: HB grade III*	2 (6)	1 (7)
Poor: HB grade VI†	1 (3)	—
Shunt-dependent hydrocephalus, total/new	4/1 (12)	1/0 (7)

Values are presented as the number of patients (%) or mean (median [range]).

* Case 1. Left 4.593-cm^3 VS, hearing preservation intended, difficult internal decompression due to anatomically narrow posterior fossa even after adequate CSF release, late identification of the FN at the brainstem and in the meatus. Case 2. Right 11.442-cm^3 VS, hearing preservation intended, atypically flattened FN visible and detectable upfront on the upper lateral aspect of the tumor capsule, indirect repeated traction and continuous exposure during resection. Case 3. Right 9.499-cm^3 VS, FN was atypically broadly flattened and spread out in several smaller fascicles at the brainstem, neurostimulation with 0.2 mA still elicited normal peripheral response. Late-onset FN palsy (HB grade III) after 2 weeks.

† Case 4. Left 10.102-cm^3 VS, preoperative FN HB grade III, FN atypically spread out over the entire medial tumor capsule, neurostimulation at the brainstem and on the tumor capsule inconsistent and diffuse. Postoperative HB grade VI without recovery, multiple reconstructive surgeries within 3–4 years after VS surgery.

However, it may be possible at the cost of larger tumor residuals amenable to adjuvant SRS, as other authors have suggested.[3,15,23,25,27,35] That strategy may also be applied to patients with serviceable hearing. Unlike the FN, we systematically skeletonized and separated the vestibulocochlear nerve from the tumor, as long as this dissection did not endanger FN integrity. However, neither the intraoperative degradation nor loss of the brainstem auditory evoked potentials was used as an indicator to stop or limit resection in our cohort.[26]

The burden of residual disease is the most important disadvantage when offering less-than-total resection to pa-

TABLE 4. Subgroup report of the 44 patients with a Koos grade IV VS from the original published cohort[26] who underwent less-than-total resection followed by a wait-and-scan protocol

	Original Cohort Short-Term FU (n = 44)*	Original Cohort Long-Term FU (n = 44)*
Mean time to last radiological FU, mos	22 (16 [0.5–72])	56 (51 [3–111])
Tumor vol at last FU, cm^3		
Mean (SD)	1 (1.4)	1 (1.9)
Median (range)	0.4 (0.0–6.1)	0.4 (0.0–8.5)
Overall volumetric outcome at last FU after STR		
Volumetrically stable: <25% change in vol	22 (50)	7 (16)
Regression: ≥25% decrease in vol	15 (34)	28 (64)
Progression: ≥25% growth in vol	7 (16)	8 (18)
Mean progression onset time, mos	31 (31 [19–50])	41 (37 [14–75])
Surgical treatment following STR		
2-stage op: early reop†	2 (5)	2 (5)
Reop	1 (2)	1 (2)
RT following STR†		
SRS: Gamma Knife, 12-Gy isodose	1 (2)	7 (58)
SRT: fractionated, 54-Gy isodose	2 (5)	5 (42)
Mean time from op to RT, mos	36 (33 [22–55])	30 (29 [5–61])
Volumetric outcome at last FU after 2nd-line RT		
Mean time to last radiological FU, mos	22 (24 [0.1–42])	77 (73 [44–111])
Volumetrically stable: <25% change in vol	2 (66)	3 (25)
Regression: ≥25% decrease in vol	0 (0)	3 (25)
Progression: ≥25% growth in vol	1 (33)	6 (50)
Mean time to last clinical FU, mos	25 (20 [0.2–75])	58 (54 [1–126])
Symptoms at last FU		
Cochlear function: serviceable hearing (AMA-CPT loss ≤50 dB)	6 (14)	6 (14)
Trigeminal nerve: normal function	38 (86)	36 (82)
FN		
Good	39 (89)	39 (89)
HB grade I	29 (66)	27 (61)
HB grade II	10 (23)	12 (27)
Fair: HB grade III	4 (9)	4 (9)
Poor: HB grade IV	1 (2)	1 (2)
Shunt dependency, total/new	6/0 (14)	6/0 (14)

Values are presented as the number of patients (%) or mean (median [range]) unless stated otherwise. Mean short-term follow-ups for radiological and clinical outcomes: 22 months and 25 months, respectively; mean long-term follow-ups: 56 and 58 months.

* Includes 3 patients from the original cohort. In 1 case, STR was performed 5 years after initial radiosurgery in an outside hospital with 54 Gy because of symptomatic regrowth of the residual. In another case, STR was performed as a second surgical procedure because of symptomatic volumetric tumor residual progression < 1 year after initial surgical debulking (71% EOR, performed by another surgeon) and ensuing adjuvant radiosurgery. In the third case, STR was performed as a second surgical procedure after initial surgery in 1988 (see Fig. 1).

† These 2 patients received early reoperations (2-stage surgery) to achieve STR and additional radiotherapy (see Fig. 1).

tients with large VSs. A wait-and-scan strategy following STR implies that the patients accept residual disease and the need for long-term monitoring.[21,25] There is, however, good scientific evidence supporting a wait-and-scan approach after STR, including the present study.[13,16,21,25,26,38] Approximately two-thirds of our patients had stable tumor residuals or residuals shrinking between the 3rd and 5th years after surgery and are still followed by a wait-and-scan regimen only. Small tumor residuals may not have a sufficient blood supply and mitotic activity to support further growth.[16,35] In these cases, postponing RT is obviously the best option.[11,20,21,24,39] Nevertheless, the growth potential of tumor residuals is not easily predictable. The risk of regrowth correlates with pre- and postoperative tumor volumes, but there is no known threshold to date. Waiting for progression implies that SRS will be applied to a larger tumor residual volume, potentially resulting in a higher morbidity.[13,16,21,25,26,38] Approximately one-third of our patients underwent second-line RT for a documented tumor residual growth within 5 years after surgery. The number of patients needing additional SRS may further increase over time, as confirmed by our Kaplan-Meier esti-

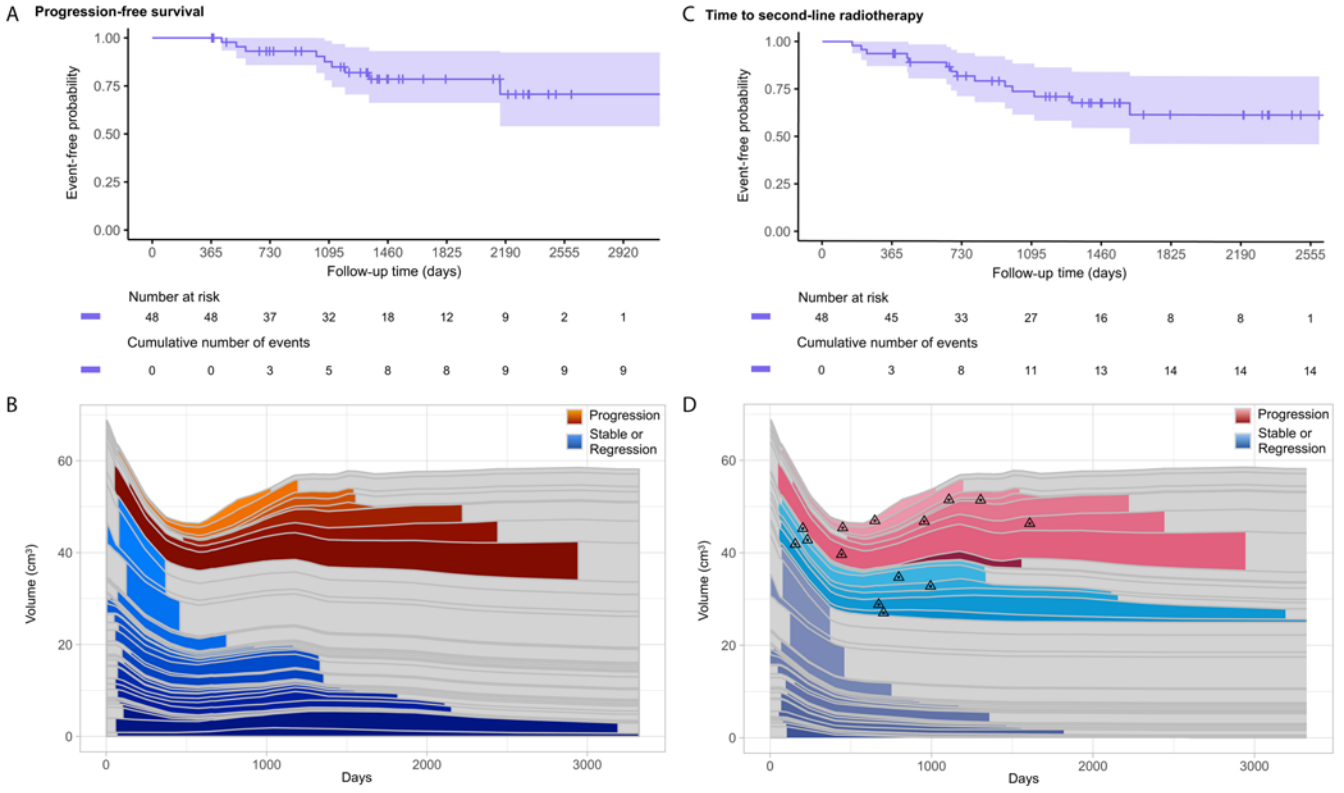

FIG. 3. Volumetric outcome after STR followed by a wait-and-scan protocol: Kaplan-Meier survival estimates (A and C) and stacked area plots (B and D) of 48 patients with a Koos grade IV VS undergoing STR stratified for the following. **A:** Volumetric progression. The probability (with the 95% CI *shaded*) of remaining progression free until a given time after the operation, together with censoring times. The corresponding number of patients still at risk and the number of events until a given time are displayed. **B:** Progressive (n = 9) and stable or regressive (n = 39) residual volumes. A ribbon is plotted for each subject corresponding to the raw scale volume at repeated visits. After the last available visit, a *gray ribbon* was plotted with a width equal to the last available measurement. *Orange/red areas* represent patients with recorded progression at the last follow-up (≥ 25% growth with respect to the first postoperative volume measurement). *Blue areas* represent patients without recorded progression at the last follow-up, being either stable (< 25% volume change) or regressive (≥ 25% volume decrease with respect to the first postoperative volume measurement). **C:** Second-line RT. The probability (with the 95% CI *shaded*) of remaining without second-line RT until a given time after the operation, together with censoring times. The corresponding number of patients still at risk and the number of events until a given time are displayed. **D:** Progressive (n = 9) and stable or regressive (n = 39) residual volumes. The *light blue* and *light pink areas* represent patients who were treated with second-line RT (n = 14), while the *dark red* and *dark blue areas* represent the volumetric course without second-line RT. The *triangles* with a *dot* inside show the time when second-line RT was initiated. The rest of the cohort is still followed up according to the wait-and-scan protocol (n = 34). In 7 of 9 (78%) patients with a progressive residual volume at the last available follow-up, second-line RT was offered within a mean time of 2.6 years (median 2.7 years, range 1.2–4.5 years). In these 7 patients, post-RT pseudoprogression was identified in 5 of 7 (71%) and post-RT progression (e.g., therapy failure) in 2 of 7 (29%) after RT. In 7 of 39 (18%) patients with a stable or regressive disease at the last available follow-up, second-line RT was offered within a mean time of 1.5 years (median 1.8 years, range 0.5–2.8 years). In all 7 patients (100%), post-RT pseudoprogression was identified.

mate, where a probability of surviving free of second-line RT was found to be up to 74% after 3 years and up to 68% after 4 years. This raises the question of whether adjuvant SRS should be performed early and in every patient (e.g., within 1 year after STR) as advocated by some authors.[20,27] Another study recently demonstrated no effect of SRS timing (earlier or later than 12 months) on tumor control, FN function, or cochlear function.[21] Single-center studies reported local control rates after SRS of 91%–100% after 10 years in tumors < 3 cm in diameter.[40] A recent meta-analysis found a pooled overall tumor control rate of 94% after approximately 4 years for SRS after STR.[20] Post-RT tumor expansion (e.g., pseudoprogression; in up to 14%), cystic degeneration (in up to 2%), local tumor scarring complicating salvage surgery, and, in exceptional cases, malignant transformation are possible complications of SRS.[41,42] Fractionation may decrease the risks of RT when treating larger volumes. Depending on the regimen, local tumor control rates up to 96% after 10 years can be expected, with a one-third regrowth rate necessitating surgical retreatment in 3% of cases.[43]

Eighty-six percent of the tumor residuals treated by second-line RT showed a post-RT pseudoprogression within a mean time of 11 months. The subsequent decrease in volume was uniformly observed within 2 years. Earlier studies have described a transient progression as part of the normal tumor response in approximately 50% of cases and a significant increase in tumor volume of > 75% after

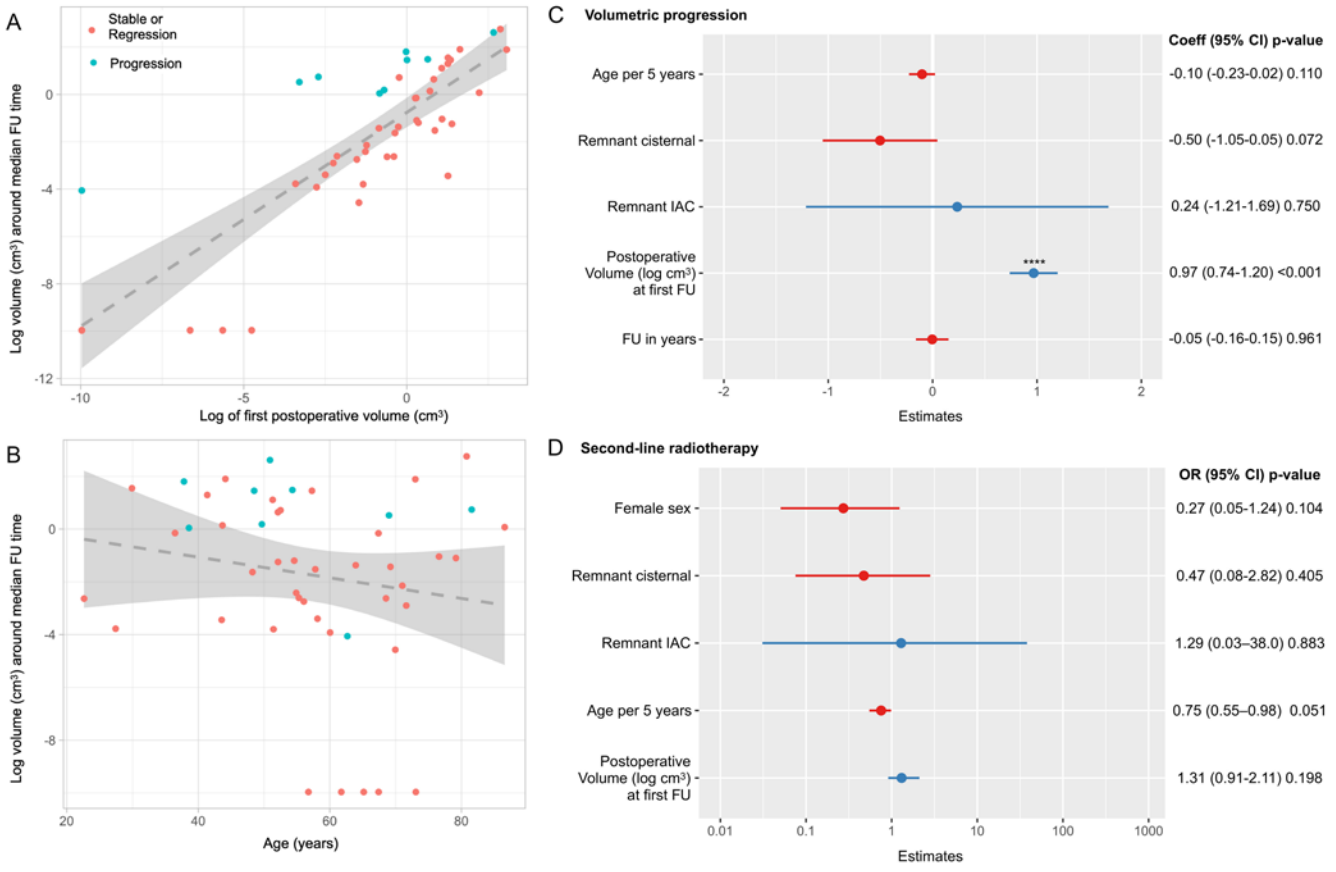

FIG. 4. Factors affecting volumetric outcome. Linear regression with the log-volume around the median follow-up time as response, stratified for the following. **A:** Logarithm of the first postoperative volume as predictor. The postoperative volume showed a statistically significant predictive power for volumetric progression with a twofold increase in the first postoperative volume predicting an increase in subsequent volumetric measurements by a factor of 1.96 (95% CI 1.67–2.30). **B:** Age as predictor. An increase in baseline age of 5 years predicts a slight decrease in subsequent volumetric measurements by a factor of 0.93 (95% CI 0.86–1.02). The model is fit by taking age in 5-year blocks. **C:** Longitudinal model of coefficient estimates for repeated measurements using generalized estimating equations of 46 patients with a Koos grade IV VS STR. Two patients were removed with missing information on tumor residual location due to a postoperative volume of 0 cm^3. The log-volume is plotted around the median follow-up time as response with the postoperative volume at the first follow-up, age in 5-year blocks, tumor residual location (reference: tumor residual location along the brainstem vs either within the cisternal portion or the internal auditory canal), and time (in years). Location of the tumor residual in the cisternal portion negatively correlated with subsequent volumetric measurements by a factor of 0.71 (95% CI 0.48–1.03), and internal auditory canal tumor residual location positively correlated with an increase by a factor of 1.18 (95% CI 0.43–3.22), when compared with a location along the brainstem. **D:** Logistic regression model of 46 patients with a Koos grade IV VS undergoing STR with radiotherapy treatment as response, including female sex (reference: male sex), tumor residual location (reference: tumor residual location along the brainstem vs either within the cisternal portion or in the internal auditory canal), age in 5-year blocks, and postoperative volume at the first follow-up. When observing a twofold increase in postoperative tumor volume, the odds for receiving second-line RT were 31% higher, with a 95% CI going from a reduction of 13% to an increase of 96%. The odds for receiving second-line RT were 25% lower for an increase in age by 5 years, with a 95% CI going from a reduction of 42% to an increase of 3%. ****$p \leq 0.0001$. Coeff = model coefficients.

SRS in up to 14%–23% of cases.[33,41] Studies have shown that 5%–10% of tumors that increase in size after SRS and remain larger at the last follow-up subsequently stop growing and remain stable in size.[32,33,42] Persistent growth after SRS has been described in 12%, with real treatment failures displaying a faster continuous growth than cases of post-RT pseudoprogression.[33] The necessity of salvage surgery in these cases remains rare.[32] In our cohort, half of the patients (15% of the total cohort) receiving second-line RT had a documented increase in volume of ≥ 25% at the last follow-up, while 2 patients (4% of the total cohort) had persistently increasing volumes, however, with 1 patient lost to follow-up due to an unrelated death event. It remains unclear whether tumor control has been achieved in these cases. If these progressive tumor residuals cause clinically relevant locoregional complications, salvage surgery might be the most likely recommended strategy.[44]

The additional risk of FN dysfunction after second-line SRS has been reported in single-center studies and is low. FN complications occur in < 5% of patients after 10 years, with tumor size, prescription dose, and the length of the irradiated nerve being risk factors for post-RT FN injury.[40] In accordance, the comparison of our original cohort[26] with the longer-term follow-up group revealed 2 (of 44,

5%) additional patients who experienced transformation from an excellent (HB grade I) to a good (HB grade II) FN function after 5 years. Longer-term SRS studies have indicated that rates of functional hearing preservation decline to 25% after 10 years.[40,41] Older age, larger tumor volume, a greater degree of baseline hearing loss, and the mean cochlear biologically effective dose (BEDGy2.47) were found to be predictive.[40,41,45] In the present cohort, patients receiving second-line RT had a hearing preservation rate of 29% after a mean of 6 years. Trigeminal nerve neuropathy rates of < 5% were found after 10 years using SRS.[40] The pons-petrous distance and the midporous transverse tumor diameter were predictive of post-RT trigeminal neuropathy.[40] From our original cohort,[26] 2 of 44 (5%) additional patients developed trigeminal nerve dysfunction after 5 years, confirming this potential delayed adverse effect when second-line RT is offered.

Limitations

Although the length of follow-up after surgery was fair, it was fairly limited for patients receiving RT, leading to a possible underestimation of morbidity and treatment failure, which may occur later.[33] The relatively small size and homogeneity of our cohort also imply that it may not be generalizable; larger cohorts and longer-term studies are certainly desirable to confirm our findings.

Conclusions

Less-than-total removal of Koos grade IV VSs with surgical emphasis on electrophysiological and neurological integrity leads to a mean resection rate of 87%, along with an excellent or good postoperative FN function in 92% of patients. A progression-free survival rate of 79% after 4 years justifies observation through a wait-and-scan approach; however, the probability of remaining free of additional treatment is 68%. Second-line RT in case of progression leads to a tumor control rate of 96% after 4.4 years with a negligible rate of additional adverse effects. So far, there was no overall treatment failure needing salvage surgery. These findings likely reflect the course of therapy the patients should expect when STR is offered.

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Disclosures

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

Author Contributions

Conception and design: Roethlisberger, Zumofen, Bodmer, Mariani. Acquisition of data: Roethlisberger, Saemann, Straumann, Neddersen, Westermann, Mariani. Analysis and interpretation of data: Roethlisberger, Moffa, Neddersen, Westermann, Mariani. Drafting the article: Roethlisberger, Rychen, Mariani. Critically revising the article: Rychen, Roethlisberger, Saemann, Straumann, Taub, Zumofen, Bodmer, Mariani. Reviewed submitted version of manuscript: Rychen, Roethlisberger, Moffa, Saemann, Taub, Neddersen, Bodmer, Mariani. Approved the final version of the manuscript on behalf of all authors: Rychen. Statistical analysis: Roethlisberger, Moffa, Neddersen, Mariani. Administrative/technical/material support: Rychen, Saemann. Study supervision: Roethlisberger, Mariani.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplemental Tables 1–9. https://thejns.org/doi/suppl/10.3171/2023.9.JNS231316.

Previous Presentations

Interim data of this study were presented as a poster presentation at the 4th Swiss Federation of Clinical Neuro-Societies Congress, Lausanne, Switzerland, October 25, 2019; as a scientific talk at the Virtual Annual Swiss Society of Neurosurgery Meeting, September 17, 2021; as a scientific short talk at the 14th Congress of the European Skull Base Society, Riva del Garda, Italy, April 22, 2022; and as a poster presentation at the Swiss Society of Oto-Rhino-Laryngology and the Swiss Society of Neuroradiology Joint Annual Meeting, Zurich, Switzerland, July 8, 2023.

Data Availability

The data supporting this study's findings are available upon reasonable request.

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