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Stereotactic radiosurgery for vestibular schwannomas in neurofibromatosis type 2: a systematic review and meta-analysis

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Abstract

Background Management of neurofibromatosis type 2 (NF2)- associated vestibular schwannomas (VSs) is challenging due to their multiplicity, early onset, proximity to the brainstem, unpredictable growth, and aggressive behavior. The optimal therapeutic intervention remains controversial in the literature, and the advantages and disadvantages of each treatment option should be evaluated for each patient. Stereotactic radiosurgery (SRS) has exhibited favorable results in the management of NF2-associated VSs. This systematic review and meta-analysis aimed to assess the role of SRS in NF2-associated VSs.

Methods On August 22, 2024, four electronic databases, comprising PubMed, Embase, Scopus, and Web of Science, were comprehensively searched. Studies that assessed SRS's radiological and clinical outcomes in NF2-associated VSs were enrolled.

Results Nineteen studies were included with 960 individuals and 1310 NF2-associated VSs. The analysis showed a pooled local control (LC) rate of 83% (95%CI:74-90%). Older age ($P=0.001$), prior resection ($P=0.003$), and lower tumor volume ($P=0.019$) were associated with higher LC rates. The results demonstrated a pooled serviceable hearing preservation (SHP) rate of 42% (95%CI:34-51%), trigeminal nerve worsening rate of 2% (95%CI:1-4%), and a facial nerve worsening rate of 5% (95%CI:2-9%). None of the patients experienced radionecrosis (RN) following SRS. Sensitivity analyses revealed a moderate to high robustness of the results. No publication bias was identified.

Conclusion SRS is an effective therapeutic modality for managing VSs, especially small—to medium-sized lesions. We showed that SRS is associated with favorable LC and SHP rates and considerably low trigeminal or facial nerve worsening and RN rates.

Keywords Stereotactic radiosurgery, Vestibular Schwannoma, Neurofibromatosis type 2, Acoustic neuroma

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Introduction

Vestibular schwannoma (VS) is a non-malignant, slow-growing cerebellopontine angle (CPA) tumor arising from Schwann cells of the vestibulocochlear nerve and encompasses approximately 10% of all CPA lesions [1–3]. The annual incidence of these lesions has been reported to be 1.09 per 100,000 cases [2, 4]. VSs usually develop unilaterally and sporadically; however, a considerable proportion of these lesions occur in the setting of neurofibromatosis type 2 (NF2) syndrome [5]. NF2 is an infrequent autosomal dominant genetic syndrome resulting from a mutation in the NF2 gene, with an incidence of 1 in 25,000, that is characterized by gradual development and subsequent growth of schwannomas of cranial nerves (CNs) and other lesions, including meningiomas [5]. Bilateral VSs are predominantly diagnosed in individuals with NF2-associated VSs who present with hearing decline and tinnitus, eventually resulting in deafness [5].

Management of NF2-associated VSs is challenging due to the significant likelihood of bilateral involvement, early onset of the disease, and proximity to the brainstem concurrent with the simultaneous presence of other tumors [5]. Several therapeutic options have been introduced for NF2-associated VSs, including observation with serial imaging studies, microsurgical resection (MS), stereotactic radiosurgery (SRS), and novel targeted therapeutic agents [5]. The optimal therapeutic intervention remained controversial in the literature, and for each patient, the advantages and disadvantages of each treatment option should be evaluated [5]. The likelihood of hearing decline is considerable in SRS or other radiotherapeutic options and MS, while the long-term outcomes following active surveillance remain unclear [5–7].

In recent decades, SRS has become a popular therapeutic option for managing VS and has been associated with promising radiological and clinical outcomes [2, 5, 8, 9]. Despite the promising outcomes of SRS in the setting of VSs, delayed treatment failure and radiation-associated adverse events, including the occurrence of new lesions or malignant transformation of the lesion, are the main concerns about the application of SRS in NF2-related VSs [5]. Several studies have assessed the efficacy of SRS in NF2-associated VSs [10–28]. This systematic review and meta-analysis was conducted to determine the effectiveness of single-session and fractionated SRS in NF2-associated VSs.

Materials and methods

Objective

This study evaluated the SRS in NF2-associated VS based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [29].

Search strategy

A systematic search was executed on August 22, 2024, utilizing customized search strategies across PubMed, Embase, Scopus, and Web of Science electronic databases. The "Radiosurgery", "Stereotactic radiosurgery", "Neuroma, Acoustic", Vestibular schwannoma", and "Neurofibromatosis 2" keywords were applied concurrently with their equivalents. The search strategy for each database is demonstrated in Supplementary Table 1. No limits regarding publication year, language, and study type were used in the systematic search of the literature.

Eligibility criteria

To establish the eligibility criteria, the subsequent PICO was designed:

- Population (P): NF2-associated VS patients.
- Intervention (I): Single-session or hypofractionated SRS modalities, including gamma knife radiosurgery (GKRS), cyberknife radiosurgery (CKRS), and linear accelerator (LINAC).
- Comparison (C): None.
- Outcome (O): Local control (LC), serviceable hearing preservation (SHP), trigeminal CN (CN V) worsening, facial nerve (CN VII) worsening, and radiation necrosis (RN).

The inclusion criteria were as follows: (1) Studies that have assessed the clinical and radiological outcomes of SRS in NF2-associated VSs, (2) Publications that reported LC, SHP, CN V or CNVII worsening, and RN, (3) Clinical trials, cohort studies, retrospective studies, or case reposts with ten or more patients, and (4) English studies. The exclusion criteria were (1) Case series with less than ten patients, case reposts, book chapters, conference abstracts, preprints, commentaries, and editorials, (2) Lack of reporting the outcome data, and (3) Inability to separate the data of NF2-associated VSs from sporadic cases, (4) Overlap between the patients of the included publications.

Study selection process

The comprehensive literature search results were imported into the Covidence software. After the duplicates were omitted, two independent reviewers (M.S. and A.K.) conducted the primary screening according to the title and abstract, and another author (B.H.) handled the disagreements. Publications that were aligned to eligibility criteria were enrolled for full-text screening. Similarly, two independent reviewers performed the full-text screening. Eventually, publications that fulfilled the eligibility requirements were included for data extraction.

Data extraction

Two authors (B.H. and S.T.) meticulously extracted the data from the included studies using a predesigned Microsoft Excel datasheet. The datasheet encompassed two main sections, including baseline characteristics of patients (Publication year, design, number of participants, number of lesions, mean age, gender, prior treatments, laterality of the lesion, and Koos grading) concurrent with SRS characteristics (Number of fractions, tumor volume, median margin dose, and isodose line) and outcome section (LC, SHP, CN V worsening, CN VII deterioration, vestibulopathy worsening, and RN). Additionally, two reviewers (B.H. and M.H.) performed the risk of bias (ROB) of the included studies based on the Risk Of Bias In Non-randomized Studies - of Interventions tool (ROBINS-1) tool [30].

Grading the quality of evidence

We evaluated the certainty of evidence for each outcome utilizing the "Grading of Recommendations, Assessment, Development, and Evaluations (GRADE)" framework. The overall quality of evidence was assessed across domains, including "Risk of bias", "Inconsistency", "Indirectness", "Imprecision", and "Publication bias". The certainty of the evidence for each pooled estimate was classified as "High", "Moderate", "Low", or "Very low" according to these criteria.

Statistical analysis

Through the application of R language (R foundation of statistical computing V R-4.4.2), the meta-analysis was performed utilizing "meta" and "metafor" packages. The heterogeneity was considered significant whenever $I^2 > 50\%$ or Cochran's Q was substantial ($p < 0.05$), and subsequently, the random-effects model was applied. The robustness of the outcomes was evaluated through the leave-one-out sensitivity analysis. Publication bias was acknowledged by visual evaluation of funnel plots and interpretation of Egger's test and trim-and-fill method. Meta-regression was performed to evaluate the possible sources of heterogeneity. A p-value < 0.05 was considered statistically significant.

Results

Study selection process

The systematic literature search through four electronic databases yielded 1395 studies (Fig. 1). Of these, 728 were determined as duplicates and omitted. The 667 studies were enrolled for title abstract screening, and among these, 128 publications met the eligibility requirements and were enrolled in the full-text screening. Of these, 109 were excluded, and 19 studies were enrolled for data extraction. It is noteworthy to mention that seven publications were excluded due to the presence of overlapping participants.

Quality assessment of the included studies

Due to their non-randomized design, the ROB assessment of the included studies was performed through ROBINS-1 (Supplementary Fig. S1). The results of the ROB evaluation showed a moderate likelihood of ROB across most of the included studies. Bias due to confounding and bias due to selection were moderate across the majority of the included studies as they were performed retrospectively. The low likelihood of the ROB across bias in the classification of interventions and bias due to deviations from intended interventions in all studies indicates reliable application of the intervention. Similarly, most studies found the ROB low to moderate across other domains.

Baseline characteristics

Nineteen studies were enrolled with 960 patients and 1310 NF2-associated VSs (Table 1). The publication year ranged from 2000 to 2024. All studies except one were conducted retrospectively (18/19). The mean age ranged from 15.2 to 40.4 years. Surgical resection was performed in 29.8% (34/1163) of lesions before SRS. Regarding the laterality, most of the cases were bilateral (70.3%, 780/1109). Approximately 52.1% (426/817) of lesions were right-sided, and 47.9% (391/817) were left-sided. The majority of the lesions were classified as Koos grade III (33.2%, 95/286) and II (32.2%, 92/286), followed by grade IV (18.5%, 53/286), and grade I (16.1%, 46/286). The mean volume ranged from 1.5 to 11.1 cc. Most lesions underwent single-session SRS (90.3%, 941/1042), while 9.7% (101/1042) were treated fractionally.

Clinical and radiological outcomes

The median follow-up duration ranged from 26 to 125 months. The included studies demonstrated that the LC rate ranged from 35 to 100%, and the SHP rate following SRS in NF2-associated VSs ranged from 9.5 to 80%. The CN V and CN VII worsening rates following SRS varied from 0 to 8.2% and 0–44%, respectively. None of the included studies reported any case of RN following SRS (Table 2).

Meta-Analysis of the outcomes

Nineteen publications were enrolled in the meta-analysis of LC (Fig. 2). The analysis showed a pooled LC rate of 83% (95%CI:74-90%) with significant heterogeneity ($I^2 = 81.8\%$, $P < 0.001$). Meta-regression identified mean age, prior resection, tumor volume, and isodose line as sources of heterogeneity (Supplementary Table 2). Older age ($P = 0.001$), prior resection ($P = 0.003$), and lower tumor volume ($P = 0.019$) were associated with higher LC

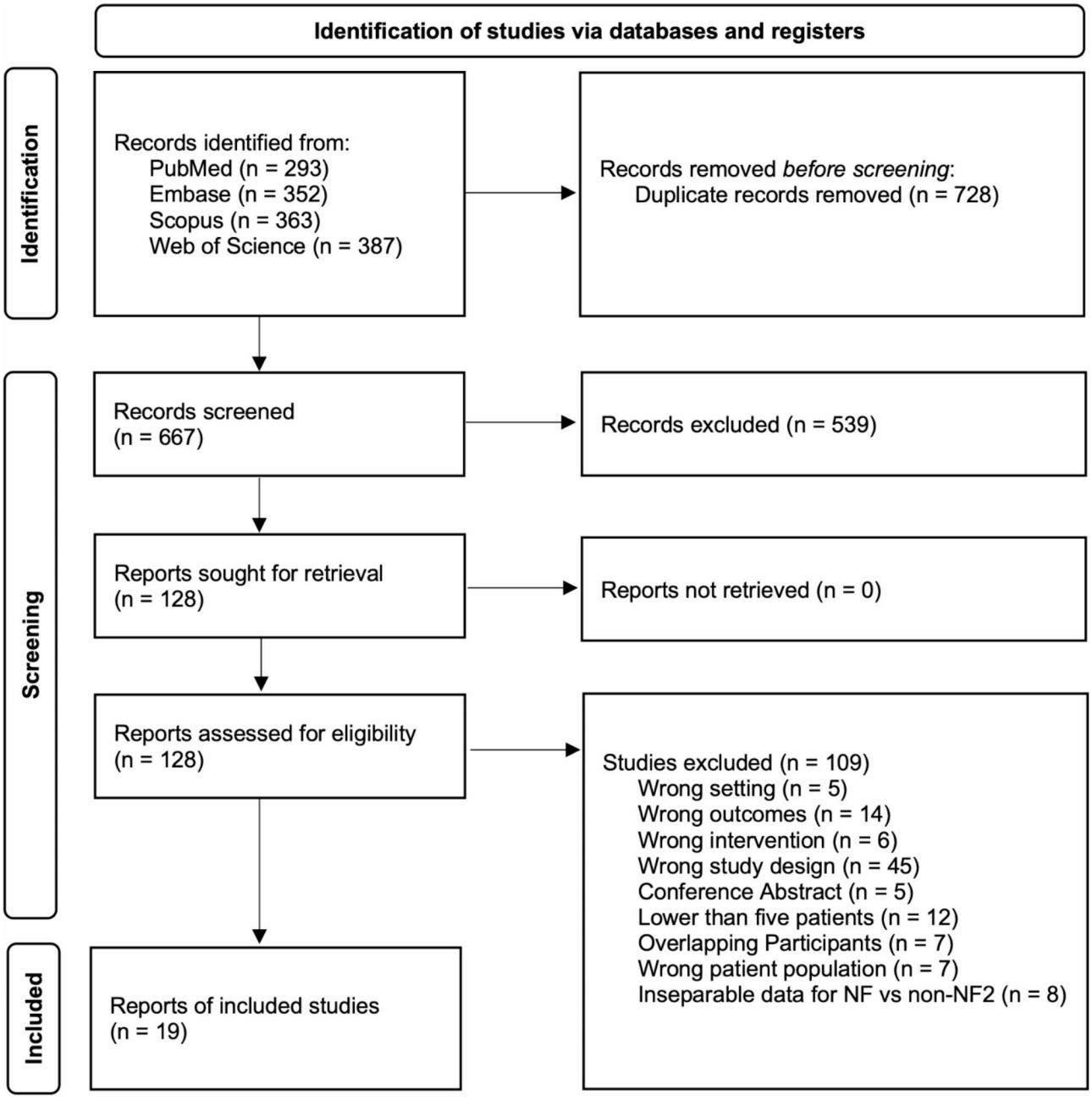

Fig. 1 The PRISMA flowchart of the current study

rates. Eighteen studies were enrolled in the meta-analysis of SHP (Fig. 3). The results demonstrated a pooled SHP rate of 42% (95%CI:34-51%) with substantial heterogeneity ($I^2 = 55.9\%$, $P = 0.002$). The meta-regression did not identify any baseline variable as a source of heterogeneity (Supplementary Table 2). Thirteen studies were included in the meta-analysis of the CN V worsening rate (Fig. 4). The meta-analysis exhibited a pooled CN V worsening rate of 2% (95%CI:1-4%) with considerable heterogeneity ($I^2 = 47.9\%$, $P = 0.02$). The meta-regression identified tumor volume as a source of heterogeneity and showed that higher tumor volumes were associated with a higher CN V worsening rate ($P = 0.02$) (Supplementary Table 2). Seventeen publications were enrolled in the meta-analysis of CN VII worsening subsequent SRS (Fig. 5). The analysis exhibited a pooled CN VII worsening rate of 5% (95%CI:2-9%) with considerable heterogeneity ($I^2 = 74\%$, $P < 0.01$). The meta-regression did not determine any baseline variable as a source of heterogeneity (Supplementary Table 2).

Table 1 Baseline characteristics of patients, lesions, and stereotactic radiosurgery

Study	Year	Country	Design (*R/P*)	Patients	Lesions	Age	Gender (M/F)	Laterality (Uni/Bi)	Side (*R*/L)	Prior Surgery (%)	Koos I/II/III/IV	SRS Fraction (S/F)	Tumor Volume (cc)	Prescribed Dose (Gy)	Isodose line (%)
Kida et al. 2000 [10]	2000	Japan	R	20	20	38.2	7/13	0/20	NA/NA	41.2	NA	20/0	NA	13	NA
Rowe et al. 2003 [11]	2003	UK	R	96	122	28.9	48/48	70/52	NA/NA	17	NA	104/18	5.2	15.2	50
Meijer et al. 2008 [12]	2008	Netherlands	R	25	50	34.2	11/14	0/50	24/26	NA	NA	45,491	2.04	11.8	80
Phi et al. 2009 [13]	2009	South Korea	R	30	36	32.8	16/14	2/34	NA/NA	20	NA	36/0	4.5	12.1	50
Sharma et al. 2010 [14]	2010	India	R	30	54	29	13/17	6/48	NA/NA	25	NA	54/0	3.7	12	50
Sun et al. 2014 [15]	2014	China	R	46	73	31.1	21/25	0/73	NA/NA	47.9	NA	NA/NA	5.1	12.9	49
Choi et al. 2014 [16]	2014	South Korea	R	17	24	15.2	NA/NA	NA/NA	NA/NA	20	NA	24/0	4.8	12.4	50
Mallory et al. 2014 [17]	2014	USA	P	26	32	37.9	16/10	22/10	NA/NA	13.5	NA	32/0	2.7	14	NA
Kim et al. 2016 [18]	2016	South Korea	R	14	20	NA	NA/NA	8/12	9/11	0	NA	45,516	NA	NA	50
Spatola et al. 2018 [19]	2018	France	R	103	129	35.6	68/61	77/26	67/62	23.1	11/39/51/28	NA/NA	1.5	12	NA
Kruyt et al. 2018 [20]	2018	Netherlands	R	34	47	40.4	21/26	34/13	23/24	25.4	10/14/10/13	47/0	3.1	11.1	60
Shinya et al. 2019 [21]	2019	Japan	R	25	30	38	6/24	20/10	NA/NA	38.8	NA	30/0	4.4	13	NA
Santa Maria et al. 2021 [22]	2021	USA	R	18	21	33	NA/NA	NA/NA	NA/NA	19.2	NA	NA	NA	NA	NA
Kim et al. 2022 [23]	2022	South Korea	R	33	41	37.5	21/12	7/34	24/17	14.6	5/15/16/5	39/3	2.8	12	50
Bin-Alamer et al. 2023 [24]	2023	USA	R	267	328	32.4	139/128	19/248	178/150	22.6	NA	328/0	NA	NA	NA
Puataweepong et al. 2023 [25]	2023	Thailand	R	25	48	32.5	8/17	0/48	25/23	39	18/15/11/4	0/48	2.3	18	71
Mauro et al. 2023 [26]	2023	Brazil	R	NA	21	NA	9/12	NA/NA	10/11	30	2/9/7/3	NA	NA	NA	NA
Sri Krishna et al. 2023 [27]	2023	India	R	85	133	29.8	55/30	13/72	66/67	19.4	NA	133/0	4.22	12	50
Shrivastava et al. 2024 [28]	2024	UK	R	66	81	37	43/38	51/30	NA/NA	16.5	NA	79/2	2.3	13	50

R/P: Retrospective/Prospective: Male: Female, Uní/Bi: Unilateral/Bilateral, R/L: Right/Left, S/F: Single/Fractionated, NA: Not available

Table 2 Clinical and radiological outcomes of the included studies

Study	LC (%)	SHP (%)	CN V worsening (%)	CN VII worsening (%)	Radionecrosis (%)	Follow-up
Kida et al. 2000 [10]	100%	33.3%	NA%	10%	0%	NA
Rowe et al. 2003 [11]	78.7%	42.2%	7.8%	14.3%	0%	51
Meijer et al. 2008 [12]	100%	40%	0%	0%	0%	51
Phi et al. 2009 [13]	66.7%	37.5%	2.8%	5.6%	0%	48.5
Sharma et al. 2010 [14]	87.5%	66.7%	0%	3.1%	0%	26.6
Sun et al. 2014 [15]	83.6%	31.9%	8.2%	5.5%	0%	109
Choi et al. 2014 [16]	35.3%	54.5%	NA%	0%	NA%	72
Mallory et al. 2014 [17]	84.4%	25%	NA%	44%	0%	91.2
Kim et al. 2016 [18]	35%	26.7%	NA%	NA%	NA%	NA
Spatola et al. 2018 [19]	90.7%	40%	3.1%	2.6%	0%	68.4
Kruyt et al. 2018 [20]	87.2%	65.2%	0%	2.5%	0%	70
Shinya et al. 2019 [21]	93.3%	50%	3.3%	6.7%	0%	121
Santa Maria et al. 2021 [22]	57.1%	NA%	NA%	NA%	NA%	NA
Kim et al. 2022 [23]	88.6%	80%	0%	0%	0%	69.1
Bin-Alamer et al. 2023 [24]	82.5%	34.9%	4%	4.9%	0%	59
Puataweepong et al. 2023 [25]	87.2%	50%	0%	0%	0%	98
Mauro et al. 2023 [26]	90.5%	9.5%	NA%	19%	0%	NA
Sri Krishna et al. 2023 [27]	80%	61%	0.8%	3.4%	0%	26
Shrivastava et al. 2024 [28]	80.2%	48.7%	1.3%	5.1%	0%	125

LC: Local control, SHP: Serviceable hearing preservation, CN: Cranial nerve, NA: Not available

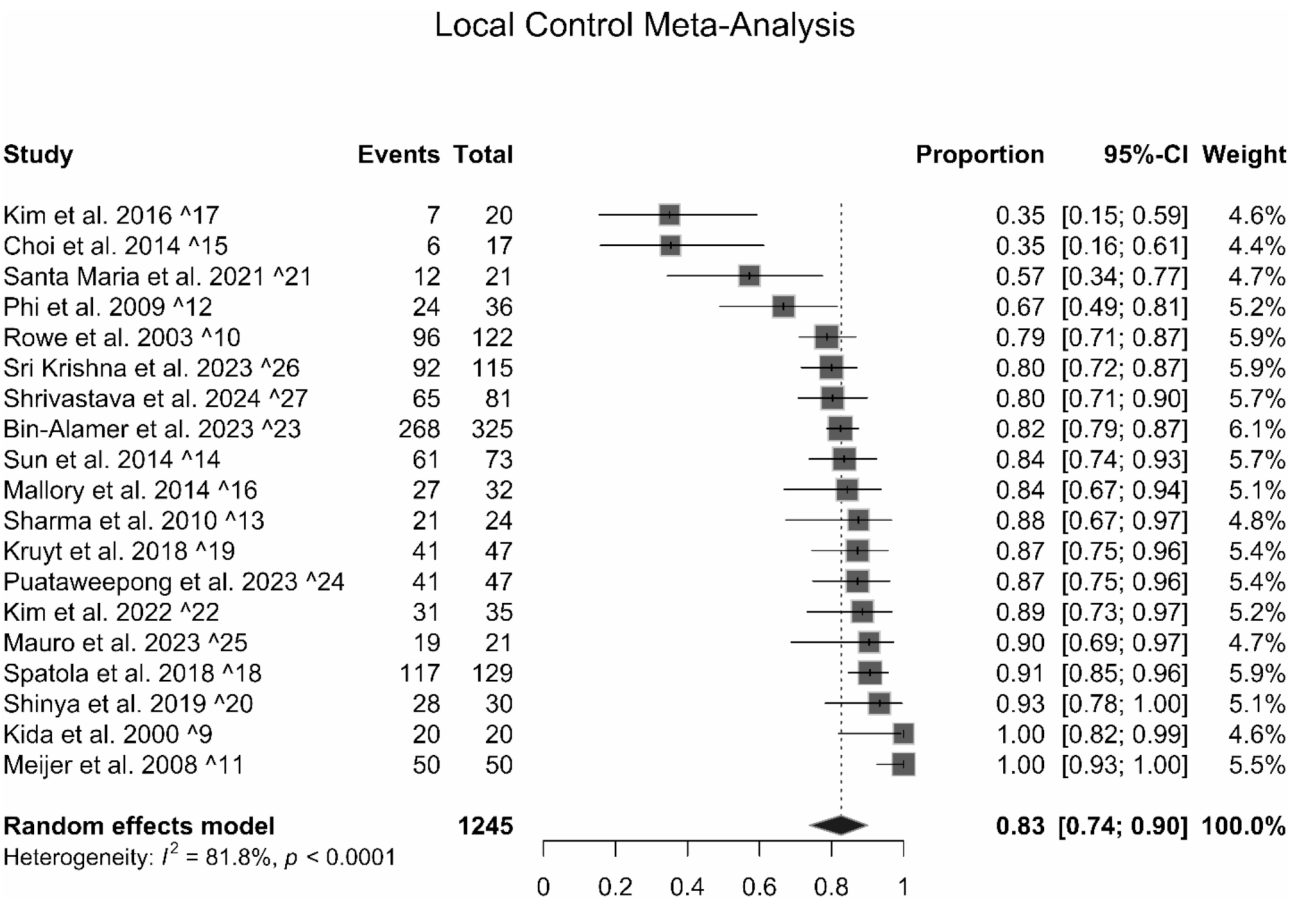

Fig. 2 Proportion meta-analysis of the local control rate following application of stereotactic radiosurgery in individuals with neurofibromatosis type 2 vestibular schwannomas

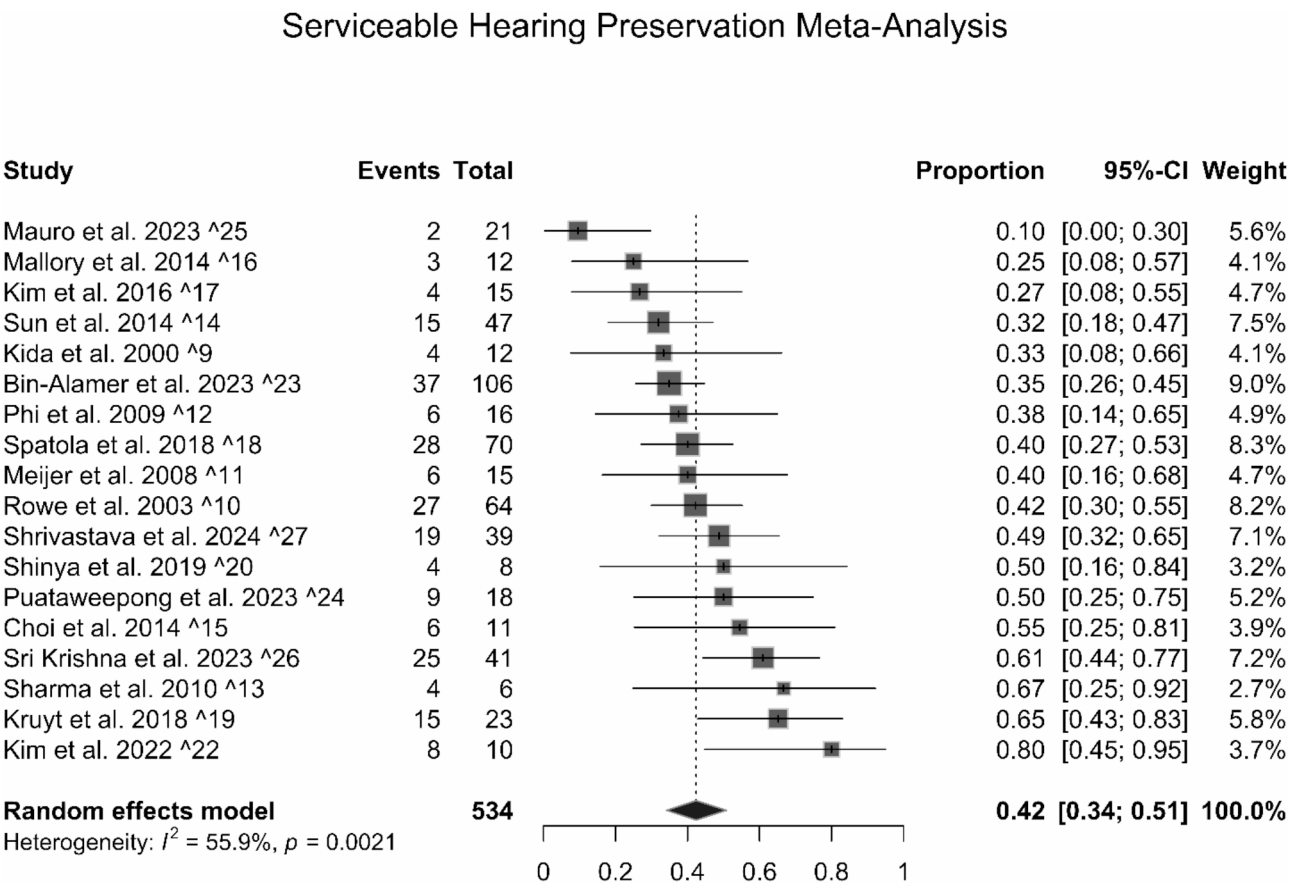

Fig. 3 Proportion meta-analysis of the serviceable hearing preservation rate following application of stereotactic radiosurgery in individuals with neurofibromatosis type 2 vestibular schwannomas

Sensitivity analysis

The sensitivity analysis for the LC demonstrated that despite high heterogeneity ($I^2 = 81.8\%$) in the meta-analysis of LC, the outcomes were robust, and the omission of each study from the analysis had a minimal effect on the overall effect (Supplementary Fig. S2). The sensitivity analysis of the SHP showed that despite substantial heterogeneity ($I^2 = 55.9\%$), the results were robust (Supplementary Fig. S3). Similarly, the sensitivity analysis of the CN V and CN VII deterioration demonstrated that the meta-analysis outcomes were robust despite the higher levels of heterogeneity and no single study had a considerable effect on outcomes (Supplementary Figs. S4-S5).

Publication Bias

The LC funnel plot demonstrated slight asymmetry levels; however, Egger's test ($P = 0.606$) demonstrated no significant possibility of publication bias (Supplementary Fig. S6). Regarding the SHP, although the funnel plot was associated with a moderate asymmetrical pattern, the Egger's ($P = 0.393$) indicated minimal likelihood of publication bias (Supplementary Fig. S7). The funnel plots of CN V and CN VII worsening were symmetrical, and the Egger's test ($P = 0.16$ and $P = 0.603$) showed a low likelihood of publication bias (Supplementary Figs. S8-S9).

Grading the quality of evidence

For LC, the evidence was of "Moderate" certainty regarding moderate ROB and high heterogeneity. SHP exhibited "Moderate" certainty, with moderate heterogeneity and modest adjustments in the trim-and-fill analysis. CN V worsening exhibited "Moderate" certainty, with considerable heterogeneity and consistent sensitivity analysis results. CN VII worsening was graded as "Moderate" certainty, mainly due to high heterogeneity and imprecision in effect estimates. Overall, the certainty of evidence was "Moderate" across the outcomes.

Subgroup Meta-Analysis based on the volume

The subgroup meta-analyses were conducted using 3 cm^3 and 4 cm^3 (Supplementary Figs. S10-S17). For LC, the subgroup analysis demonstrated a higher proportion of local control in smaller tumor volumes as the proportion for ≤ 3 was 0.90 [95% CI: 0.79–0.97], while for > 3, it was 0.79 [95% CI: 0.65–0.90]; however, the difference was not significant ($p = 0.076$) (Supplementary Fig. S10). Similarly,

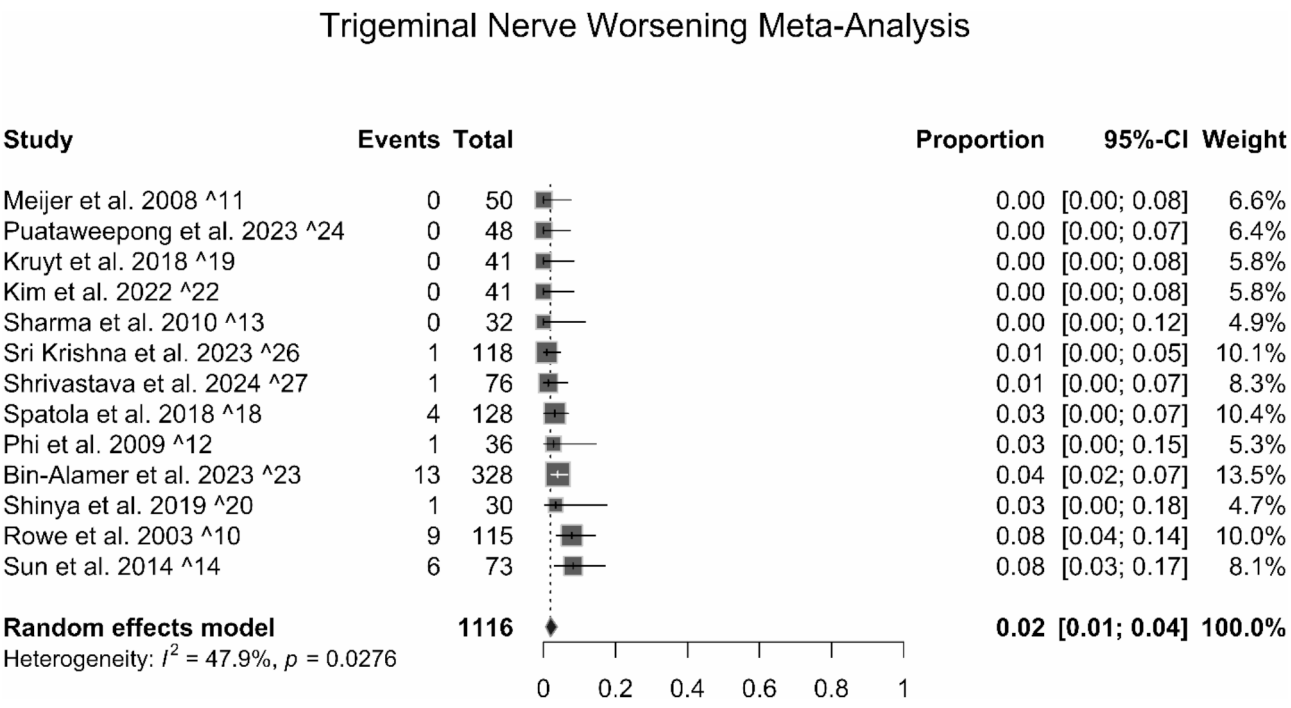

Fig. 4 Proportion meta-analysis of the trigeminal nerve worsening rate following application of stereotactic radiosurgery in individuals with neurofibromatosis type 2 vestibular schwannomas

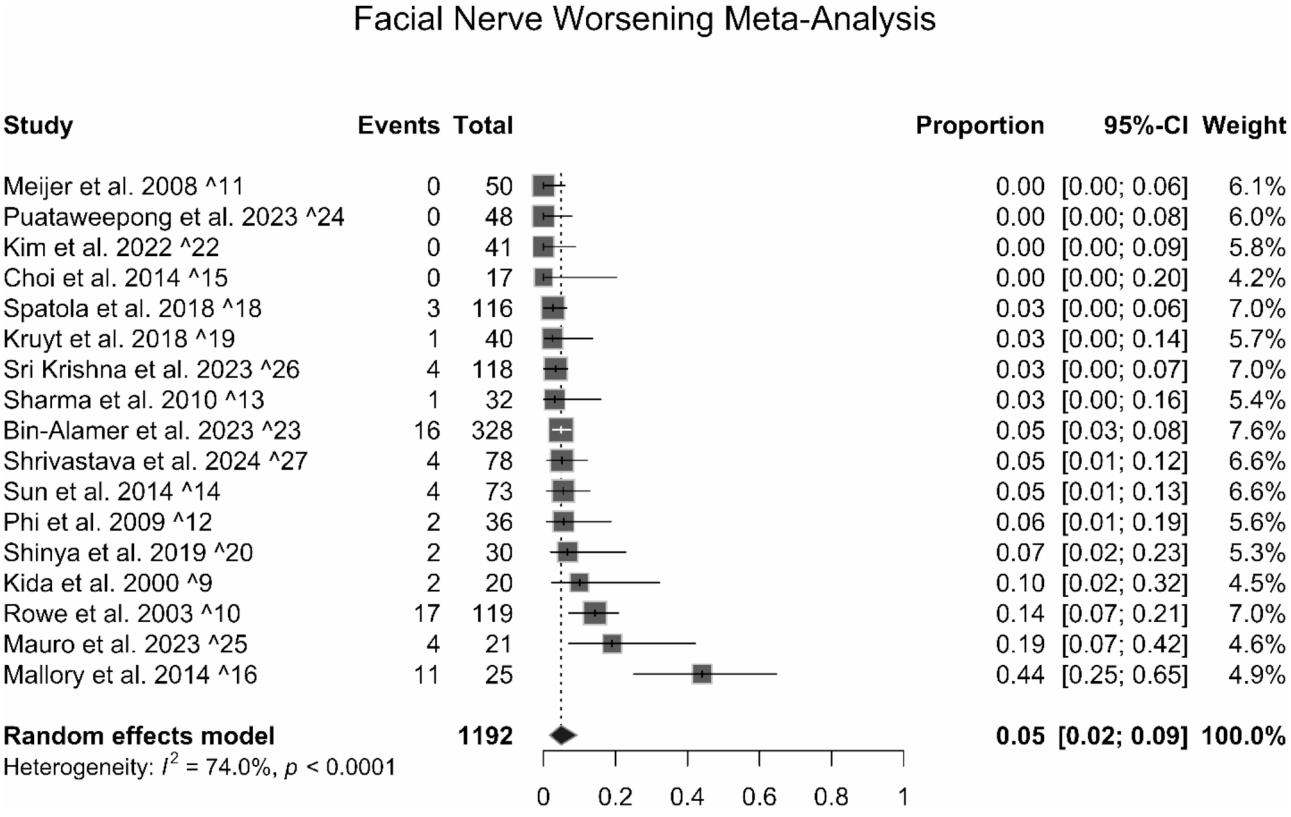

Fig. 5 Proportion meta-analysis of the facial nerve worsening rate following application of stereotactic radiosurgery in individuals with neurofibromatosis type 2 vestibular schwannomas

the proportion for ≤ 4 was 0.89 [95% CI: 0.82–0.95], compared to > 4 at 0.76 [95% CI: 0.55–0.92]; however, the difference was not significant ($p = 0.059$) (Supplementary Fig. S11). For SHP, the proportion for ≤ 3 was 0.44 [95% CI: 0.37–0.52], compared to > 3 at 0.47 [95% CI: 0.40–0.54], with no significant subgroup differences ($p = 0.62$) (Supplementary Fig. S12). In the ≤ 4 vs. >4 subgroups, the SHP proportion for ≤ 4 was 0.48 [95% CI: 0.40–0.55], while for > 4 it was 0.44 [95% CI: 0.37–0.52], also without significant subgroup differences ($p = 0.52$) (Supplementary Fig. S13).

For CN V deterioration, smaller tumor volumes were associated with lower worsening rates. The proportion for ≤ 3 was 0.01 [95% CI: 0.00–0.03], compared to > 3 at 0.03 [95% CI: 0.00–0.07], with insignificant differences ($p = 0.1534$) (Supplementary Fig. S14). Regarding the 4 cm^3 cut-off, the proportion for ≤ 4 was 0.01 [95% CI: 0.00–0.02], while for > 4 it was 0.04 [95% CI: 0.01–0.10], with significant differences ($P = 0.015$) (Supplementary Fig. S15). The subgroup analysis showed lower worsening rates in smaller tumor volumes for CN VII deterioration. The proportion for ≤ 3 was 0.04 [95% CI: 0.00–0.21], while for > 3, it was 0.06 [95% CI: 0.04–0.08], with no significant differences ($p = 0.76$) (Supplementary Fig. S16). In the ≤ 4 vs. >4 subgroups, the proportion for ≤ 4 was 0.04 [95% CI: 0.00–0.13], compared to > 4 at 0.06 [95% CI: 0.02–0.11], with a p-value of 0.0529 for subgroup differences (Supplementary Fig. S17). These findings underscore the considerable impact of tumor volume on clinical outcomes and its importance in treatment decision-making.

Discussion

This systematic review and meta-analysis highlighted the impact of SRS in the management of NF2-associated VSs concurrent with insignificant compilation rates. Our results suggested that SRS is accompanied by LC and SHP rates of 83% and 42% concurrent with CN V and CN VII deterioration rates of 2% and 5% without any RN occurrence. Our results were aligned with the prior meta-analysis that showed an LC rate of 88% concurrent with an odds ratio of 0.26, 1.62, and 1.42 for serviceable hearing worsening, increase in facial and trigeminal nerve impairment following SRS in NF2-associated VSs [5].

The management of NF2-associated VSs is challenging due to the multiplicity of lesions, unpredictable growth patterns, and aggressive behavior [5, 18]. NF2-associated VSs are correlated with more unfavorable radiological and clinical outcomes in composition with sporadic VSs [18]. Phenotypical classes of NF2 patients are another factor correlated with unpredictable clinical courses [5]. Wishart phenotype is a phenotype of these patients that results in an early onset disease course that frequently manifests in the early 20s. In comparison, the Feiling-Gardner phenotype usually presents in the 50–60 s [5]. In addition to more rapid growth than sporadic cases, the VSs tend to occur bilaterally in the setting of NF2, and prior investigations proposed a three to six-year interval between the diagnosis of the first and the contralateral VS [31, 32]. Another challenge with the VSs in the setting of NF2 is the multiplied likelihood of the development of other lesions encompassing schwannoma and meningioma and a significantly higher risk of malignant transformation [5, 33].

Individuals with NF2-related and sporadic VS showed remarkable differences in outcomes [20, 21, 34]. NF2 individuals are typically associated with greater complication rates, as Mahboubi et al. showed significantly higher complication rates (8.8% vs. 4.4%, $P < 0.01$), CN VII complications (32.3% vs. 16.8%, $P < 0.01$), and length of stay (5 vs. 4, $P < 0.01$) [34]. Resection in NF2-associated cases is more challenging, with a lower complete resection rate and greater recurrence likelihood regarding the necessity of nerve preservation and the genetic predisposition to tumor development [20, 21, 34]. On the other hand, sporadic VS usually has more favorable surgical and functional outcomes, with higher gross total resection achievement and hearing preservation [20, 21, 34]. For SRS, both NF2 and sporadic VS demonstrated similar long-term tumor control rates (10-year rate of 92%); however, the overall survival is lower in NF2 individuals (73% vs. 97%, $P = 0.005$) because of other tumors progression [21]. Hearing preservation rates are similar following SRS yet decline more swiftly in NF2 patients [21]. These variations highlight the significance of personalized treatment strategies tailored to the different pathophysiological and clinical features of NF2-related and sporadic cases.

MS has been the primary therapeutic option for managing NF2-associated VSs associated with favorable LC rates [18, 35]. However, MS is correlated with a considerable negative effect on the quality of life of these individuals regarding hearing function and related complications [18]. Frequent therapeutic interventions required by NF2-associated VS patients during their lifetime is another issue with MS, as due to their invasiveness, it may exacerbate the hardship of the disease [21]. SRS is another therapeutic option for NF2-associated VSs, a non-invasive option associated with favorable outcomes with relatively low complications, especially for small to medium-sized lesions [2, 8, 9, 36]. The primary objective for SRS is the induction of tumor growth arrest, while MS is performed to achieve a gross total resection [20]. Despite favorable tumor control outcomes, SRS and MS modalities are associated with unfavorable hearing outcomes [5, 8, 13].

Following SRS in NF2-associated VSs, the LC and SHP rates have been reported to range from 10 to 100% and 10–80%, respectively [10–28]. Several studies with considerable sample size evaluated the outcomes of SRS for VSs in the setting of NF2 [11, 19, 24, 27]. Bin-Alamer et al. assessed the impact of SRS in 267 patients with 328 NF2-associated VSs, which were bilateral in 75.6% of cases, and 75.3% of cases had simultaneously other tumors [24]. The median margin, maximum, and cochlear doses were 12 Gy, 24 Gy, and 5 Gy, respectively [24]. They demonstrated that in a median follow-up of 59 months, no malignant transformation or radion-induced lesions were developed concurrent with 10- and 15-year local control rates of 77% and 52%, respectively [24]. They also showed a 5- and 10-year SHP rate of 64% and 35%, with facial and trigeminal nerve worsening rates of 4.9% and 4% [24]. They also stated that age and bilaterality predict serviceable hearing loss [24]. Sri Krishna et al. evaluated 85 individuals with 133 NF2-associated VS [27]. The mean tumor volume, margin dose, and maximum dose were 4.22 cm^3, 12 Gy, and 24.36 Gy, respectively [27]. They demonstrated a tumor control rate at 12-, 24-, 60-, and 108-months of 100%, 84%, 75%, and 55% concurrent with an SHP rate of 61.7% [27]. Shrivastava et al. evaluated 81 NF2-associated VSs and demonstrated a 5- and 10-year tumor control rate of 77% and 71% and an SHP rate of 49% at the last follow-up [28]. In their study, 5- and 10-year SHP rates were 69% and 53%, and they also showed that lesions larger than 3 cm and increasing genetic severity are associated with more unfavorable outcomes [28]. Mauro et al. retrospectively evaluated the role of SRS in 34 patients with 54 NF2-associated VSs [26]. In a median follow-up period of 62.6 months, they showed a tumor control rate of 90.5% and a mean progression-free survival rate of 57.2 months for single-fraction SRS [26]. New hearing loss, facial palsy, tinnitus, and vestibulopathy rates were 9.5%, 19%, 0%, and 0% in their study [26].

Our findings showed that the SHP rate following SRS in NF2-associated VSs ranged from 9.5 to 80%, with a pooled SHP rate of 42% [10–28]. On the other hand, several studies have evaluated the hearing outcomes in sporadic VS cases. Carlson et al. reported an SHP rate of 80% at 1 year and 23% at 10 years in a cohort of 44 patients [37]. In another study by Johnson et al., the hearing preservation rate was 77.8% and 51.8% at 3- and 10-year time points [38]. A study by Paek et al. reported an SHP rate of 52% in 25 patients with sporadic VS [39]. Niranjan et al. reported an SHP rate of 64.5% in 79 patients with sporadic VS [40]. Generally, the SHP rate is greater in sporadic cases than in NF2-associated individuals. The underlying cause is that sporadic cases are often unilateral and less aggressive clinical behavior with a smaller size and a minimal impact on peripheral structures. In contrast, NF2-related cases tend to be bilateral and have greater damage to the surrounding nerves, as well as the progressive effect of the NF2 mutation.

Study limitations

Our study possesses several limitations. First, most enrolled publications were performed retrospectively, introducing a considerable likelihood of selection and reporting bias. Another limitation is the presence of substantial heterogeneity in the meta-analysis that resulted from heterogeneity in the tumor volume, SRS fractions, SRS doses, and prior treatments. Several studies were associated with short-term follow-up duration that may impact the results for LC and SHP; however, NF2-associated VSs require considerable observation. Prospective and randomized clinical trials with more participants and long follow-up duration are necessary to confirm our findings.

Conclusion

Management of NF2-associated VSs is challenging due to their early onset, multiplicity, unpredictable growth, and aggressive clinical course. SRS is an effective therapeutic modality in managing VSs, especially small to medium-sized lesions. We showed that SRS is accompanied by favorable LC and SHP and considerably low CN V or CN VII worsening and RN rates. Early intervention should be conducted to achieve the maximal advantages of SRS. Further prospective studies with larger sample sizes are needed to confirm our findings.

Abbreviations

NF2	Neurofibromatosis type 2
VS	Vestibular schwannomas
SRS	Stereotactic radiosurgery
LC	Local control
SHP	Serviceable hearing preservation
RN	Radionecrosis
CN	Cranial nerve
CPA	Cerebellopontine angle
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
GKRS	Gamma knife radiosurgery
CKRS	Cyberknife radiosurgery
LINAC	Linear accelerator
ROB	Risk of bias
ROBINS-1	Risk Of Bias In Non-randomized Studies - of Interventions tool
R/P	Retrospective/Prospective: Male: Female
Uni/Bi	Unilateral/Bilateral
R/L	Right/Left
S/F	Single/Fractionated
NA	Not available

Supplementary Information

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Supplementary Material 1

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval
The study is deemed exempt from receiving ethical approval.

Consent to participate
Not applicable.

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Competing interests
The authors declare no competing interests.

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