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Treatment options for unilateral vestibular schwannoma: a network meta-analysis

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Abstract

This study aimed to explore the effect of observation, microsurgery, and radiotherapy for patients with vestibular schwannoma (VS). We searched PubMed, Medline, Embase, Web of Science, and Cochrane library from their establishment to July 31, 2024. 34 non-RCTs and 1 RCT that included 6 interventions were analyzed. We found the MS, and different SRS all had better tumor local control rates. Regarding preserved hearing, the order from the highest to the lowest was FSRT 5 fractions, FSRT 3 fractions, SRS, ConFSRT, Observation, and MS. Regarding improvement in the rate of tinnitus, the order from the highest to the lowest was ConFSRT, FSRT 3 fractions, SRS, Observation, MS, and FSRT 5 fractions. In terms of improving the rate of disequilibrium/vertigo, the order from the highest to the lowest was SRS, Observation, FSRT 3 fractions, FSRT 5 fractions, MS, and ConFSRT. In terms of protection of the trigeminal nerve, the order from the highest to lowest was observation, SRS, ConFSRT, FSRT 3 fractions, FSRT 5 fractions, and MS. Lastly, in terms of protection of the facial nerve, the order from the highest to lowest was SRS, ConFSRT, Observation, FSRT 3 fractions, FSRT 5 fractions, and MS. In patients with VS, MS and radiosurgery showed better local tumor control rates; however, compared with MS, different SRS all provided better protection of nerve function and improved the symptoms of vestibular function and tinnitus, among which the best was SRS. Therefore, in these patients, SRS may be a promising alternative treatment.

Keywords Vestibular schwannoma, Microsurgery, Stereotactic radiosurgery, Fractionated stereotactic radiotherapy, Conventionally fractionated stereotactic radiotherapy

What's new?

Current treatment options for VS are divided into three categories as follows: microsurgery, radiotherapy, and observation. Unfortunately, all these options have inherent risks, and the vestibular function is inevitably compromised. Moreover, in the literature, there is a relative lack of relevant studies directly comparing these three treatment regimens. In this study, we conducted a network meta-analysis to explore the advantages and disadvantages of surgery, radiotherapy, and observation. It found that in patients with VS, MS and radiosurgery showed better local tumor control rates than observation; however, compared with MS, different SRS all provided better protection of nerve function and improved the symptoms of vestibular function and tinnitus, among

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which the best was SRS. Therefore, in patients with unilateral VS, SRS may be a promising alternative treatment.

Background

Vestibular schwannoma (VS), also known as acoustic neuroma, is a benign Schwann cell-derived tumor originating from the vestibulocochlear nerve [1]. It accounts for approximately 8% of intracranial tumors and is the most common tumor in the cerebellopontine angle region, with an annual incidence of 10.4/1000,000 [2]. With the advances in imaging technology and increased access to magnetic resonance imaging, more VS cases are being diagnosed, allowing for the detection of VS at an early stage when the tumor is smaller [3, 4].

Owing to its deep location, which is adjacent to the brain stem and cerebellum, and its close relationship with important structures such as the trigeminal nerve, facial nerve, cochlear nerve, and posterior cranial nerve, when the tumor, including benign ones, persists or grows continuously, it can become invasive and compress the surrounding structures. This results in the development of various clinical symptoms, with more than 60% of patients with VS having progressive hearing loss and tinnitus [5]. Large tumors can also cause hydrocephalus and brain stem compression, which can lead to facial paresthesia, vertigo, headache, and other symptoms, thus seriously affecting the patient's daily activities and quality of life [6, 7].

Current treatment options for VS are divided into three categories as follows: microsurgery (MS), radiotherapy, and observation [8–12]. Unfortunately, all these options have inherent risks, and the vestibular function is inevitably compromised, as the tumor originates from the vestibular nerve. In particular, in radiotherapy, tumors and their potentially deleterious effects on vestibular function are not eliminated, and the simultaneous exposure of vestibular organs and vestibular nerves to radiation may cause additional vestibular toxicity [13, 14]. In observation treatment, the tumor is left in situ, and vestibular function may deteriorate owing to the natural course of the disease. Therefore, the main goal of VS treatment is not only to improve vestibular symptoms but also to prevent future complications due to tumor progression.

Nonetheless, the reported effects of VS treatment on vestibular symptoms are diverse. Some studies have reported no significant difference in the development of vestibular symptoms in patients with VS undergoing surgery, radiotherapy, or observation treatment, whereas others have noted a reduction in the incidence of vestibular symptoms after surgery [15, 16]. In the long term, because of the central compensation of unilateral VS, regardless of the treatment strategy used, vestibular symptoms are expected to be relieved. However, the current treatment options for these symptoms are mainly based on the tumor size, presence of tumor growth, age of the patient, hearing ability, complications, and patient selection. These three treatment options are supported by level II or III quality of evidence only, and there is a lack of high-level evidence to support which treatment option is the most advantageous [17]. Moreover, in the literature, there is a relative lack of relevant studies directly comparing these three treatment regimens.

This study aimed to conduct a network meta-analysis to explore the advantages and disadvantages of surgery, radiotherapy, and observation as treatment options for VS patients from the aspects of tumor control rate and vestibular function.

Patients and methods

Study design

The systematic review and network meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist for network meta-analysis. This network meta-analysis study was registered with PROSPERO under the registration number: CRD42024574320.

Search strategy

The following retrieval formula was used: ((((((((((((((((((single dose radiosurgery) OR (single dose)) OR (radiosurgical)) OR (radiosurgically)) OR (stereotactic radiation therapy)) OR (stereotactic radiation therapies)) OR (stereotactic radiotherapy)) OR (stereotactic radiotherapies)) OR (stereotactic radiosurgery)) OR (stereotactic radiosurgeries)) OR (gamma knife)) OR (linacs)) OR (particle)) OR (accelerators)) OR (particle accelerators)) OR (linac)) OR (linear accelerator)) OR (CyberKnife)) OR (radiosurgery)) AND ((((((((((vestibular schwannoma) OR (vestibular schwannomas)) OR (acoustic neuroma)) OR (acoustic neuromas)) OR (acoustic schwannoma)) OR (acoustic schwannomas)) OR (acoustic neurilemoma)) OR (acoustic neurilemomas)) OR (acoustic tumor)) OR (acoustic tumors)) OR (acoustic neurinoma)) OR (acoustic neurinomas)). Medline, PubMed, Web of Science, Embase, and Cochrane Library were searched from their establishment until July 31, 2024. Moreover, we also manually searched the published articles (such as, systematic reviews, meta-analysis), some unpublished trials, which was registried in the World Health Organization clinical registries, and so on.

Inclusion and exclusion criteria

We made the criteria of inclusion and exclusion, which were based on the PICOS strategy (P: patient/population, I: intervention, C: comparison/control, O: outcome, S: study design). In terms of patients, the aged ≤ 70 years with newly diagnosed unilateral VS. In terms of interventions, studies with treatment options, including involved

stereotactic radiosurgery (SRS), fractionated stereotactic radiotherapy (FRST), gamma knife surgery (GKS), microsurgery (MS), and conservative management (CM), were included. In terms of study design, randomized controlled clinical trials or non-randomized controlled clinical trials were included. In terms of outcomes: the outcome indicators were local control rate of tumor, preserved hearing, trigeminal nerve toxicity, facial nerve toxicity, tinnitus, vertigo/disequilibrium.

The exclusion criteria were as follows: type 2 neurofibromatosis, trials including patients with other types of tumors (such as meningeoma, craniopharyngioma, metastatic encephaloma, etc.), pregnant women, lactating patients, patients had severe complications and could not tolerate treatment, single-arm trials, single case reports, protocol, and animal experiments.

Study endpoints

The outcome measures were local control rate of the tumor, preserved hearing, trigeminal nerve toxicity, facial nerve toxicity, tinnitus, vertigo/disequilibrium.

Data screening and quality evaluation

The literature-retrieval results were screened by two reviewers, independently. And then, they assessed all randomized trials based on six aspects by using the Cochrane quality evaluation method, and evaluated all non-randomized trials by using the Newcastle–Ottawa Scale (NOS). If there had some problems or disagreements during the process, we can resolve by two reviewers discussion or consulted by a third person. At last, we also assessed the evidence quality in our analysis by using Grading of Recommendations Assessment and Development and Evaluation (GRADE) framework.

Data extraction

The data of all included studies were extracted, including the name of first or corresponding author, the year of publication, nation, study type, age of the patients, intervention indicators, total number in each intervention group, the treatment details, and local control rates and rates of preserved hearing, trigeminal nerve toxicity, facial nerve toxicity, tinnitus, and disequilibrium/vertigo in patients with VS in different treatment groups. If data were missing, we contacted the authors of this study wherever possible.

Statistical analysis

Before making the network meta-analysis, we performed a heterogeneity test, transitivity and consistency test for all the included studies. The fixed-effects model was adopted when $p>0.1$ and $I^2<50\%$, which means the results were non-heterogeneous. Otherwise, the heterogeneous was adopted the random-effects model. The clinical and methodological variables (such as: sex, age, the percent of male, the tumor size and the tumor volume) were compared between the different interventions for transitivity. We also used a two-tailed statistical test, $p<0.05$ was considered statistically significant. In the network meta-analysis, the surface under the cumulative ranking curve was used to rank the outcome measures. We also performed a consistency test by using the node-splitting method. The software of RevMan version 5.3 (Cochrane Collaboration, London, UK) and Stata 16.0 (StataCorp, Texas, USA) were performed to statistical analyses.

Results

Literature search results

Figure 1 presents a flow diagram of the literature search and inclusion of relevant studies. The initial search identified 10,820 studies, of which 8642 duplicates were excluded by screening the title and abstract. Then, 2178 studies were screened by reading the research objective and study type, as a result, 1985 studies were excluded (not relevant, letter to editors or commentary, review articles, animal experiments, and case reports, and so on). Of the 193 studies, 110 were excluded because they were not published in English, lacking the main outcome indicators, not control group, and so on. Finally, after excluding 48 studies due to without outcome indicators, inappropriate results, included patients with other tumors. 35 were analyzed in this network meta-analysis.

All were retrospective or prospective studies [6–14, 18–42], except for one randomized control trial [16]. Of the included studies, 15 were published in the USA, 5 in Germany, 3 in Norway, 2 in Canada, 2 in Korea, 1 in France, 1 in Netherlands, 1 in Thailand, 1 in Australia, 1 in Belgium, 1 in Japan, 1 in Singapore, and 1 in Sweden. The percent of sex in our analysis also has no statistically significant difference (95% CI: [−22.52, 11.49], $p>0.05$). More details on the included studies, including the study design, publication year, and type of interventions, are shown in Tables 1 and 2. The total sample size was 5069 cases and included 6 interventions (SRS, ConFSRT, FSRT 5 fractions, MS, FSRT 3 fractions, and observation treatment).

Quality evaluation

The non-randomized trials ($n=34$) were assessed using the NOS based on selection, comparability, and outcome, with a total score of >5, indicating high quality (Table 3). Meanwhile, the randomized controlled trial (RCT) was assessed by the Cochrane risk of bias tool, revealing the use of the correct randomization method, use of the correct blinding method in the conduct of the study and the assessment of the results, complete outcome data, and no

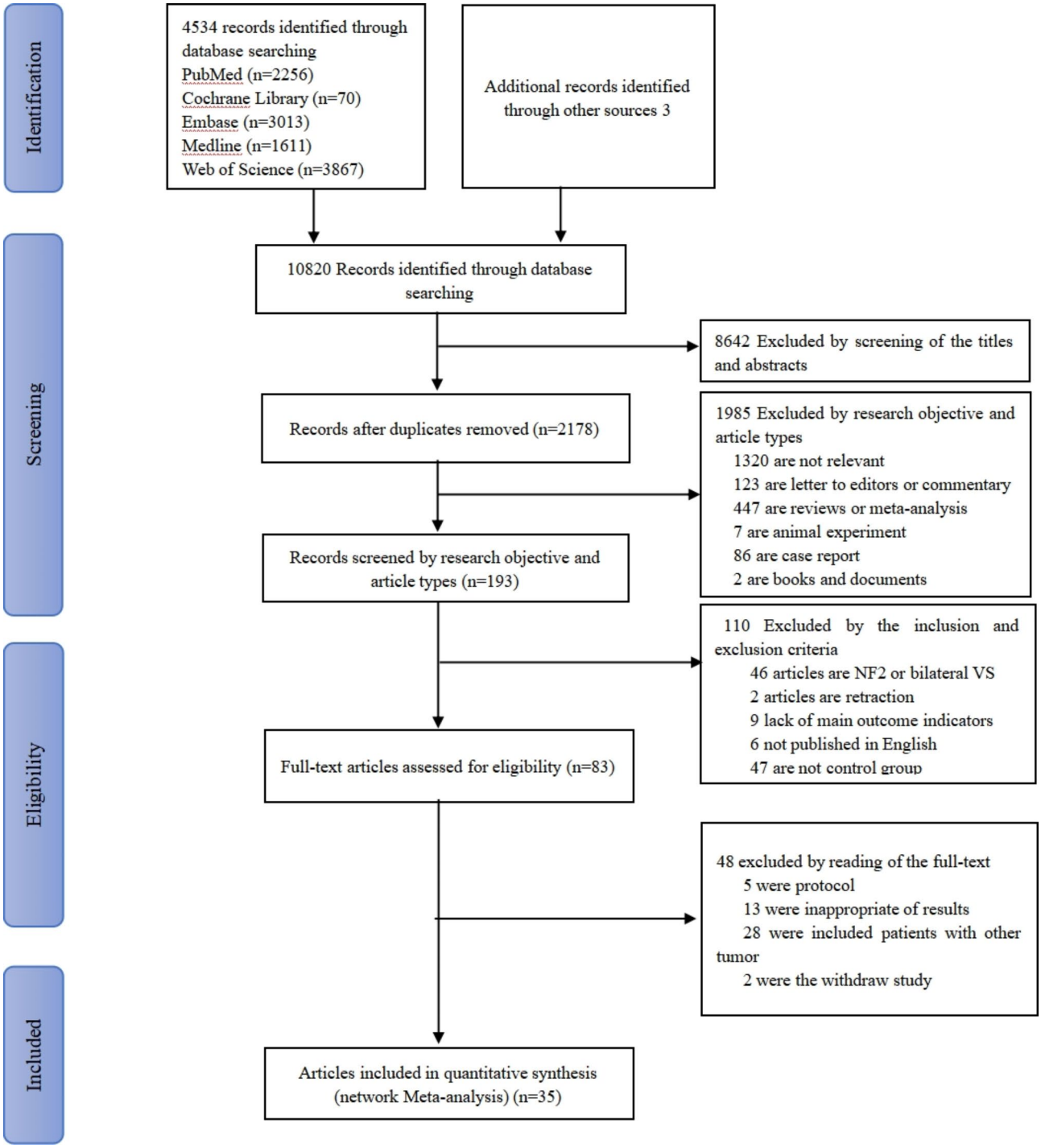

Fig. 1 Flow chart of the study selection process

selective reporting. Therefore, the included RCT trial was of high quality.

Traditional meta-analysis

Subgroup analysis was performed on 30 studies reporting local tumor rates in patients with VS after treatment with different interventions (Supplementary Fig. 1a). Owing to significant heterogeneity, a random-effects model was used (I^2>50%, p<0.1). Compared with FSRT 5 fractions (*RR*: 1.01, *95% CI*: 0.98–1.04, P=0.61), FSRT 3 fractions (*RR*: 0.97, *95% CI*: 0.86–1.09, P=0.60), ConFSRT (*RR*: 0.99, *95% CI*: 0.97–1.02, P=0.68), and MS (*RR*: 1.02, *95% CI*: 0.98–1.06, P=0.32), SRS was not significantly associated with higher local tumor rates. There was also no

Table 1 Baseline characteristics of involved patients

Study	Country	Publication year	Age(y)	Male (I/C%)	Cases	Outcomes	Follow-up time
Söderlund Diaz L	Sweden	2020	61.0/63/60.5	57%/41%/52%	37/39/60	LC, hearing preservation, adverse effect	41/76/56 months
Régis J	France	2002	61/52	35%/46%	100/110	LC, hearing preservation, adverse effect	3/5 years
Pollock BE	USA	2006	53.9/48.2	58.6%/52.8%	46/36	Hearing preservation, adverse effect	42 months
Myrseth E	Norway	2009	57.5/52.5	43.3%/42.8%	60/28	Hearing preservation, adverse effect	2 years
Anderson BM	USA	2014	NR	NR	48/37/19	LC, hearing preservation, adverse effect	83.6/43.1/53.6 months
McWilliams W	USA	2011	73/67.5	NR	13/10	LC	15/12.5 months
Barnes JH	USA	2021	61 ± 11/52 ± 14/61 ± 10	46%/48%/46	78/118/48	Hearing preservation, adverse effect	2.1 years
Breivik CN	Norway	2013	55.7/57.7	46.3%/46.9%	124/113	LC, hearing preservation, adverse effect	55 months
Chung HT	Canada	2004	52/62	NR	27/45	LC, hearing preservation	26/27 months
Chung LK	USA	2018	59.7/65.3	50.0%/35.7%	24/14	LC, hearing preservation	45.1/38.3 months
Coelho DH	USA	2008	71/53	41.7%/40%	12/10	LC, adverde effect	40.2/45.5 months
Combs SE	Germany	2015	60	55%	291/169	LC, hearing preservation	67 months
Han MS	Korea	2020	51/53	38.1%/40%	21/30	LC, hearing preservation, adverse effect	77/89 months
Henzel M	Germany	2009	60	NR	35/39	LC, hearing preservation	50/36 months
Dhayalan D	Norway	2023	54/54	54%/62%	48/50	LC, hearing preservation, adverse effect	4/4 years
Karpinos M	USA	2002	62.5/48	31.5%/26.1%	73/23	LC, hearing preservation, adverse effect	48/24 months
Kopp C	Germany	2011	63.2/56	53.0%/44.5%	68/47	LC, hearing preservation, adverse effect	30.1/32.1 months
Lo A	Canada	2018	65/55	44%/33%	136/71	LC, adverse effect	5 years
Meijer OW	Netherlands	2003	63/43	49%/57%	49/80	LC, hearing preservation, adverse effect	30/35 months
Patel KS	USA	2019	62/54	56%/46%	43/57	LC, hearing preservation, adverse effect	24 months
Pua-taweepongP	Thailand	2013	47/50/39	18%/37%/50%	39/79/28	LC, hearing preservation	5/5/5 years
Singh R	USA	2019	60.5	40.6%	12/52	LC, hearing preservation	49.45/29.6 months
Huo M	Australia	2020	57/64	52.6%/71.4%	19/14	LC	28.7/30.2 months
Schneider T	USA	2016	63/56	45%/53.2%	40/122	LC	1.7/5.3 years
Slane BG	USA	2017	62/61/53.5	66.7%/52.3%/30%	15/21/20	LC, adverse effect	3.3/4.3/6.6 years
Udawatta M	USA	2019	65.4/61.3/56.1	47.6%/66.7%/45.5%	21/6/33	LC, hearing preservation, adverse effect	31/9/41 months
Tatagiba M	Germany	2023	59.0/47.45	43%/46%	559/342	LC, hearing preservation, adverse effect	7/7 years
Collen C	Belgium	2011	59/57	34%/24%	78/41	Hearing preservation, adverse effect	56/73 months
Park CE	Korea	2011	59.7 ± 10.8/49.9 ± 10.8	45.2%/40%	31/15	LC, hearing preservation, adverse effect	43.8/49.4 months
Golfinos JG	USA	2016	54.1/50.6; 58.7/57.9; 59.0/58.0	52.4%/47.6%; 49.4%/55.4%; 41%/39%	21/21; 83/83; 85/85	LC, hearing preservation, adverse effect	30.3/43.7 months 19.0/35.7 months 20.0/36.8 months

Table 1 (continued)

Study	Country	Publication year	Age(y)	Male (I/C%)	Cases	Outcomes	Follow-up time
Kessel KA	Germany	2017	63/59	41.1%/44.5%	56/128	Hearing preservation, adverse effect	7.5 years
Khattab MH	USA	2019	74/58.5/65	50%/33.4%/35.5%	12/12/31	LC	2 years
Shirato H	Japan	1999	55.5 ± 15.6/52.0 ± 15.0	26%/38.2%	27/50	LC, hearing preservation, adverse effect	35/31 months
Wong RX	Singapore	2018	53.7	NR	46/31	LC, hearing preservation, adverse effect	40.6 months
Andrews DW	USA	2001	61/57	47.8%42.8%	69/56	LC, hearing preservation, adverse effect	119 ± 67/115 ± 96 months

* LC: Local control, NR: Not report

significant difference when MS compared with FSRT 3 (*RR*: 1.00, *95% CI*: 0.86–1.17, $P = 1.00$) and FSRT 5 fractions (*RR*: 1.04, *95% CI*: 0.90–1.21, $P = 0.58$), respectivelly and between those undergoing ConFSRT and FSRT 5 fractions (*RR*: 1.00, *95% CI*: 0.90–1.12, $P = 0.96$). However, compared with the patients receiving observation treatment, those receiving SRS (*RR*: 1.82, *95% CI*: 1.57–2.12, $P < 0.00001$) and ConFSRT (*RR*: 1.86, *95% CI*: 1.25–2.76, $P = 0.002$) had better local tumor control rates.

Subgroup analysis was performed on 26 studies reporting preserved hearing in patients with VS after treatment with different interventions (Supplementary Fig. 1b). Owing to significant heterogeneity, a random-effects model was used ($I^2 > 50\%$, $p < 0.1$). Compared with FSRT 5 fractions (*RR*: 1.04, *95% CI*: 0.92–1.18, $P = 0.49$), FSRT 3 fractions (*RR*: 0.98, *95% CI*: 0.53–1.79, $P = 0.94$), ConFSRT (*RR*: 0.91, *95% CI*: 0.76–1.08, $P = 0.28$), and observation treatment (*RR*: 0.90, *95% CI*: 0.76–1.07, $P = 0.23$), SRS was not significantly associated with the preservation of hearin. Compared with the observation treatment and FSRT 5 fractions (*RR*: 0.89, *95% CI*: 0.56–1.42, $P = 0.63$), ConFSRT (*RR*: 1.74, *95% CI*: 0.87–3.48, $P = 0.12$) showed no significant difference. However, compared with the observation treatment, MS was significantly associated with improvement in preserved hearing (*RR*: 0.56, *95% CI*: 0.43–0.73, $P < 0.0001$).

Subgroup analysis was performed on 16 studies reporting tinnitus in patients with VS after treatment with different interventions (Supplementary Fig. 1c). Owing to significant heterogeneity, a random-effects model was used ($I^2 > 50\%$, $p < 0.1$). Compared with FSRT 3 fractions (*RR*: 1.05, *95% CI*: 0.37–2.98, $P = 0.92$), FSRT 5 fractions (*RR*: 0.87, *95% CI*: 0.55–1.37, $P = 0.54$), ConFSRT (*RR*: 0.90, *95% CI*: 0.75–1.07, $P = 0.24$), MS (*RR*: 1.27, *95% CI*: 0.91–1.78, $P = 0.16$), and observation treatment (*RR*: 1.03, *95% CI*: 0.86–1.24, $P = 0.74$), SRS was not significantly associated with the occurrence of tinnitus. There was also no significant difference in the development of tinnitus between patients treated with MS and observation treatment (*RR*: 1.06, *95% CI*: 0.59–1.89, $P = 0.85$) and between those undergoing ConFSRT and FSRT 5 fractions (*RR*: 0.57, *95% CI*: 0.17–1.88, $P = 0.35$).

Subgroup analysis was performed on 16 studies reporting disequilibrium/vertigo in patients with VS following different treatment interventions (Supplementary Fig. 1d). Owing to significant heterogeneity, a random-effects model was used ($I^2 > 50\%$, $p < 0.1$). Compared with FSRT 3 fractions (*RR*: 0.68, *95% CI*: 0.33–1.37, $P = 0.28$), FSRT 5 fractions (*RR*: 0.67, *95% CI*: 0.39–1.16, $P = 0.15$), MS (*RR*: 1.18, *95% CI*: 0.86–1.62, $P = 0.31$), ConFSRT (*RR*: 0.81, *95% CI*: 0.56–1.18, $P = 0.28$), and observation treatment (*RR*: 1.07, *95% CI*: 0.74–1.54, $P = 0.71$), SRS was not significantly associated with the development of disequilibrium/vertigo. There was no significant difference in the occurrence of disequilibrium/vertigo between patients treated with MS and observation treatment (*RR*: 1.57, *95% CI*: 0.96–2.56, $P = 0.07$) and between those treated with ConFSRT and FSRT 5 fractions (*RR*: 1.15, *95% CI*: 0.13–10.13, $P = 0.90$).

Subgroup analysis was performed on 15 studies reporting trigeminal nerve toxicity in patients with VS undergoing different treatment interventions (Supplementary Fig. 1e). Owing to unobserved heterogeneity, a fixed-effects model was used ($I^2 < 20\%$, $p > 0.1$). Compared with FSRT 3 fractions (*RR*: 0.63, *95% CI*: 0.16–2.46, $P = 0.51$), FSRT 5 fractions (*RR*: 0.86, *95% CI*: 0.38–1.94, $P = 0.71$), ConFSRT (*RR*: 1.37, *95% CI*: 0.86–2.19, $P = 0.18$), and MS (*RR*: 0.70, *95% CI*: 0.16–3.04, $P = 0.63$), SRS was not significantly associated with the development of trigeminal nerve toxicity. There was no significant difference in the occurrence of trigeminal nerve toxicity between patients undergoing ConFSRT and FSRT 5 fractions (*RR*: 0.68, *95% CI*: 0.16–3.02, $P = 0.62$) or observation treatment (*RR*: 1.04, *95% CI*: 0.67–1.62, $P = 0.87$).

Lastly, subgroup analysis was performed on 19 studies reporting facial nerve toxicity in patients with VS following different treatment interventions (Supplementary Fig. 1f). Owing to significant heterogeneity, a

Table 2 Overview of the included literature

Study	Publication year	Study design	Study Type	Intervention Control	Tumor size Mean(cm)	Tumor volume Mean (cm^3)	Treatment details
Söderlund Diaz L	2020	Retrospective study	Single institution	SRS FSRT 3 fractions FSRT 5 fractions	1.5 1.5 1.5	0.5 1.1 1.7	SRS (12 Gy), FSRT in 3 fractions for a total of 18–21 Gy [6 Gy×3–7 Gy×3], FSRT in 5 fractions (5 Gy×5).
Régis J	2002	Prospective study	Single institution	SRS MS	NR NR	NR NR	SRS was used the GammaPlan software, the peripheral doses were 12–14 Gy, MS was used translabyrinthine approach or middle fossa approach.
Pollock BE	2006	Prospective study	Single institution	SRS MS	1.2 1.4	NR NR	SRS was used the GammaPlan software, the peripheral doses were 12–14 Gy, MS was used translabyrinthine approach or middle fossa approach
Myrseth E	2009	Prospective study	Single institution	SRS MS	1.6 1.8	NR NR	SRS (12 Gy), MS was used translabyrinthine approach
Anderson BM	2014	Retrospective study	Single institution	SRS FSRT 5 fractions ConFSRT	1.7 1.5 1.8	1.35 0.89 2.94	SRS (12.5 Gy), FSRT in 5 fractions (4 Gy×5), ConFSRT: of 45-Gy at 1.8 Gy/Fraction.
McWilliams W	2011	Retrospective study	Single institution	SRS FSRT 5 fractions	1.1 1.4	NR	SRS (12.5 Gy), FSRT in 5 fractions (5 Gy×5)
Barnes JH	2021	Prospective study	Single institution	Observation MS SRS	NR	NR	SRS (12.5 Gy), MS was used retrosigmoid, translabyrinthine, middle fossa, and transotic approaches.
Breivik CN	2013	Prospective study	Single institution	Observation SRS	NR NR	1.2 3.9	SRS: doses were 12 Gy
Chung HT	2004	Retrospective study	Single institution	ConFSRT SRS	1.6 2.0	2.6 2.4	ConFSRT: of 45-Gy at 1.8 Gy/Fraction, SRS (12 Gy)
Chung LK	2018	Retrospective study	Single institution	ConFSRT SRS	NR NR	2.53 1.44	ConFSRT: of 45-Gy at 1.8 Gy/Fraction, SRS (12 Gy)
Coelho DH	2008	Retrospective study	Single institution	SRS MS	1.2 1.4	NR NR	SRS (12 Gy), MS was used translabyrinthine approach
Combs SE	2015	Retrospective study	Multicenter	ConFSRT SRS	1.5	NR	ConFSRT: of 57.6 Gy at 1.8 Gy/Fraction, SRS (13 Gy)
Han MS	2020	Retrospective study	Single institution	MS SRS	1.5 1.3	NR	MS was used retrosigmoid approaches, SRS: doses was 12 Gy
Henzel M	2009	Retrospective study	Single institution	SRS ConFSRT	NR NR	NR NR	ConFSRT: of 54.0 Gy at 1.8 Gy/Fraction, SRS (13 Gy)
Dhayalan D	2023	Randomized clinical trial	Single institution	SRS Observation	NR NR	0.76 0.51	SRS (12 Gy)
Karpinos M	2002	Retrospective study	Single institution	SRS MS	NR NR	NR NR	SRS: doses were 14.5 Gy, MS was used translabyrinthine, suboccipital, and middle fossa approaches.
Park CE	2011	Retrospective study	Single institution	SRS MS	1.9 3.5	NR NR	SRS: doses were 14.5 Gy, MS was used translabyrinthine, suboccipital, and middle fossa approaches.
Kopp C	2011	Retrospective study	Single institution	SRS ConFSRT	NR NR	1.24 5.79	SRS (12 Gy), ConFSRT: of 54.0 Gy at 1.8 Gy/Fraction
Lo A	2018	Retrospective study	Single institution	SRS ConFSRT	2.1 2.0	2.9 3.6	SRS (12 Gy), ConFSRT: of 50.0 Gy at 1.8 Gy/Fraction
Meijer OW	2003	Prospective study	Single institution	SRS FSRT 5 fractions	2.6 2.5	NR NR	SRS (10 Gy or12 Gy), FSRT in 5 fractions (4 Gy×5–5 Gy×5)
Patel KS	2019	Retrospective study	Single institution	SRS ConFSRT	1.7 1.9	NR NR	SRS (12 Gy), ConFSRT: of 50.0 Gy at 1.8 Gy/Fraction
Pua-taweepong P	2013	Prospective study	Single institution	SRS FSRT 5 fraction ConFSRT	1.6 2.5 4	0.96 3.9 9.5	SRS (12 Gy), FSRT in 5 fractions (4 Gy×5–5 Gy×5), ConFSRT: of 50.0 Gy at 1.8 Gy/Fraction

Table 2 (continued)

Study	Publication year	Study design	Study Type	Intervention Control	Tumor size Mean(cm)	Tumor volume Mean (cm^3)	Treatment details
Singh R	2019	Prospective study	Single institution	SRS FSRT 5 fraction	NR NR	1.09	SRS (12 Gy), FSRT in 5 fractions (4 Gy×5–5 Gy×5)
Huo M	2020	Retrospective study	Single institution	SRS FSRT 5 fraction	NR NR	4.06 6.71	SRS (12 Gy), FSRT in 5 fractions (5 Gy×5)
Schneider T	2016	Retrospective study	Single institution	SRS FSRT 5 fraction	NR NR	1.03 0.96	SRS (12 Gy), FSRT in 5 fractions (5 Gy×5)
Slane BG	2017	Retrospective study	Single institution	SRS FSRT 5 fraction ConFSRT	1.14 1.7 2.0	NR NR NR	SRS (12.5 Gy), FSRT in 5 fractions (5 Gy×5), ConFSRT: of 54.0 Gy at 1.8 Gy/Fraction
Udawatta M	2019	Retrospective study	Single institution	SRS FSRT 5 fraction ConFSRT	NR NR NR	1.3 1.4 1.8	SRS (12 Gy), FSRT in 5 fractions (5 Gy×5), ConFSRT: of 50.4 Gy at 1.8 Gy/Fraction
Tatagiba M	2023	Retrospective study	Single institution	SRS MS	NR NR	NR NR	SRS (12–13 Gy), MS was used retrosigmoid approach
Collen C	2011	Retrospective study	Single institution	SRS ConFSRT	1.66 2.46	1.7 6.3	SRS (12.5 Gy), ConFSRT: of 50.0 Gy at 1.8 Gy/Fraction
Golfinos JG	2016	Retrospective matched cohorts	Single institution	SRS MS	1.0;1.2;1.2 1.0;1.22;1.22	NR NR	SRS (13 Gy), MS was used translabyrinthine, retrosigmoid, and middle cranial fossa craniotomies approach
Kessel KA	2017	Prospective study	Single institution	SRS ConFSRT	1.03 3.55	NR NR	SRS (12 Gy), ConFSRT of 54 Gy at 1.8 Gy/Fraction
Khattab MH	2019	Retrospective study	Single institution	SRS FSRT 3 fraction FSRT 5 fraction	0.745 1.42 2.13	NR NR NR	SRS (12.5 Gy), FSRT in 3 fractions for a total of 18–21 Gy (7 Gy×3), FSRT in 5 fractions (5 Gy×5).
Shirato H	1999	Retrospective study	Single institution	Observation ConFSRT	1.56 ± 0.72 1.7 ± 9.0	NR NR	ConFSRT: of 44.0 Gy at 1.8 Gy/Fraction
Wong RX	2018	Retrospective study	Single institution	SRS FSRT 5 fraction	NR NR	1.18 3.12	SRS (12.5 Gy), FSRT in 5 fractions (5 Gy×5).
Andrews DW	2001	Retrospective study	Single institution	SRS ConFSRT	NR NR	2.92 ± 2.6 2.78 ± 2.4	SRS (12 Gy), ConFSRT of 50 Gy at 2.0 Gy/Fraction

* SRS: Stereotactic radiosurgery, FSRT: Fractionated stereotactic radiotherapy, MS: Microsurgery, ConFSRT: Conventionally-fractionated stereotactic radiotherapy, NR: Not report

random-effects model was used ($I^2 > 20\%$, $p < 0.1$). Compared with FSRT 3 fractions (*RR*: 0.45, *95% CI*: 0.13–1.62, $P = 0.22$), FSRT 5 fractions (*RR*: 0.84, *95% CI*: 0.38–1.86, $P = 0.66$), ConFSRT (*RR*: 1.64, *95% CI*: 0.95–2.84, $P = 0.07$), and observation treatment (*RR*: 0.18, *95% CI*: 0.02–1.50, $P = 0.11$), SRS was not significantly associated with the development of facial nerve toxicit. However, compared with MS, SRS (*RR*: 0.12, *95% CI*: 0.02–0.72, $P = 0.02$) could reduce the incidence of facial nerve toxicity. There was no significant difference in the occurrence of facial nerve toxicity between ConFSRT and FSRT 5 fractions (*RR*: 0.21, *95% CI*: 0.01–4.11, $P = 0.30$) or observation treatment (*RR*: 0.68, *95% CI*: 0.04–10.28, $P = 0.78$).

The assessment of evidence quality in this analysis

We also evaluated the quality in this analysis by using the GRADE. We found that the credibility of the evidence was moderate or very low in the aspects of local tumor rates, improved preserved hearing, improved tinnitus, improved disequilibrium/vertigo, reduced tigeminal nerve toxicity, and reduced facial nerve toxicity for the observation study. The reason for these ratings of evidence quality were mainly driven by the design of study and the indirectness comparisons between several interventions (supplementary Table 1a). The credibility of the evidence was moderate in the aspects of local tumor rates, improved preserved hearing, improved tinnitus, and improved disequilibrium/vertigo for the RCT. The reason for these ratings of evidence quality were mainly due to the indirectness comparisons between several interventions and the small sample size (supplementary Table 1b).

Network meta-analysis

Network diagram of different intervention measures

A direct comparison is shown if there is a direct line between the two intervention groups, otherwise, the absence of lines indicates a lack of evidence for direct

Table 3 Quality assessment of the non-RCT studies

Study	Selection	Comparability	Outcome	Total Score
Söderlund Diaz L	4	2	3	9
Régis J	4	2	3	9
Pollock BE	4	1	3	8
Myrseth E	4	1	3	8
Anderson BM	4	2	3	9
McWilliams W	4	1	3	8
Barnes JH	4	2	2	8
Breivik CN	4	2	2	8
Chung HT	4	1	2	7
Chung LK	4	1	1	6
Coelho DH	4	2	1	7
Combs SE	4	2	2	8
Han MS	4	1	2	7
Henzel M	4	2	2	8
Karpinos M	4	1	3	8
Park CE	4	2	3	9
Kopp C	4	2	3	9
Lo A	4	2	3	9
Meijer OW	4	2	3	9
Patel KS	4	2	3	9
Puataweepong P	4	1	2	7
Singh R	4	1	2	7
Huo M	4	1	2	7
Schneider T	4	2	2	8
Slane BG	4	2	3	9
Udawatta M	4	2	2	8
Tatagiba M	4	2	2	8
Collen C	4	2	2	8
Golfinos JG	4	2	2	8
Kessel KA	4	2	3	9
Khattab MH	4	1	3	8
Shirato H	4	1	3	8
Wong RX	4	2	3	9
Andrews DW	4	2	3	9

comparison. The size of the dots represents the sample size, and the thickness of the lines represents the number of study items. The SRS, ConFSRT, and FSRT 5 fractions had the largest sample sizes and the largest number of entries in direct or indirect comparative trials (Fig. 2).

Transitivity

In this analysis, we also made a transitivity in the aspects of percent of male, age, tumor size, and tumor volume (supplementary Fig. 2a-d). We found that, there were no significant differences in baseline of the percentage of male patients, mean age, and tumor size for most comparisons. And there were slightly differences in baseline tumor volume for most comparisons.

Inconsistency test

Because both direct and indirect evidence were available, an inconsistency test was required, prior to the integration analysis. We found no inconsistency in the network meta-analysis, and the difference was not statistically significant ($p>0.05$), that is, the direct and indirect evidence included could be combined (Supplementary Fig. 3).

Sequence diagram

The rate of tumor local control from the highest to lowest was MS, FSRT 3 fractions, ConFSRT, FSRT 5 fractions, SRS, and observation treatment, indicating that except for the observation treatment, the rate of tumor local control was good in the other five interventions (Fig. 3a). In terms of preserved hearing, the order from highest to lowest was FSRT 5 fractions, FSRT 3 fractions, SRS, ConFSRT, observation treatment, and MS, indicating that SRS is associated with a higher rate of preserved hearing than observation treatment (Fig. 3b).

Regarding the improved rate of tinnitus, the order from the highest to lowest was ConFSRT, FSRT 3 fractions, SRS, Observation, MS, and FSRT 5 fraction (Fig. 3c). This indicates that radiosurgery is associated with a lower rate of tinnitus. Regarding the improved rate of disequilibrium/vertigo, the order from the highest to lowest was SRS, observation treatment, FSRT 3 fractions, FSRT 5 fractions, MS, and ConFSRT. SRS had a lower rate of disequilibrium/vertigo than the observation treatment, and the other four interventions had a higher rate (Fig. 3d). In terms of improving trigeminal nerve toxicity, the order from the highest to lowest was observation treatment, SRS, ConFSRT, FSRT 3 fractions, FSRT 5 fractions, and MS. Compared with the observation treatment, the other four interventions had higher trigeminal nerve toxicity (Fig. 3e). Lastly, in terms of improving facial nerve toxicity, the order from the highest to lowest was SRS, ConFSRT, observation treatment, FSRT 3 fractions, FSRT 5 fractions, and MS (Fig. 3f). Compared with MS, SRS had better facial nerve protection.

Discussion

VS is a benign but potentially devastating tumor with aggressive growth and is associated with significant complications (including deafness and lesions of the facial nerve) [43]. Thus, it is necessary to seek effective interventions for VS. Historically, surgical resection has been a valued treatment option because complete resection represents the greatest degree of tumor control [44]. However, owing to the anatomical relationship between VS and multiple cranial nerves, surgical resection needs to be very precise and fine. Some studies have shown that the decline in cranial nerve function after surgical treatment can have serious clinical consequences in patients with VS [45]. Hence, researchers have explored other alternative treatment options, such as SRS, surgical excision is different, the main purpose of which is to control

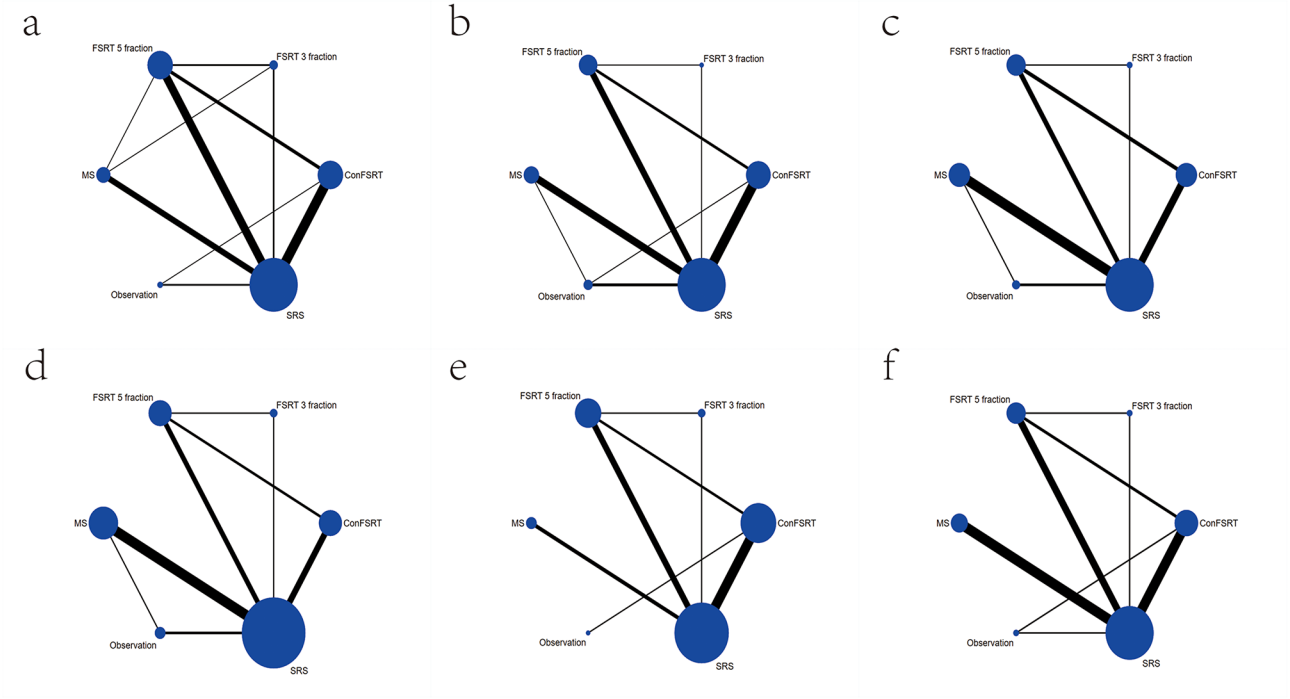

Fig. 2 Network Chart, **a**: Network chart based on the local control tumor rates in patients with VS, **b**. Network chart based on the preserved hearing in patients with VS, **c**. Network chart based on the improved tinnitus in patients with VS, **d**. Network chart based on the improved disequilibrium/vertigo in patients with VS, **e**. Network chart based on the reduced trigeminal nerve toxicity in patients with VS, **f**. Network chart based on the reduced facial nerve toxicity in patients with VS

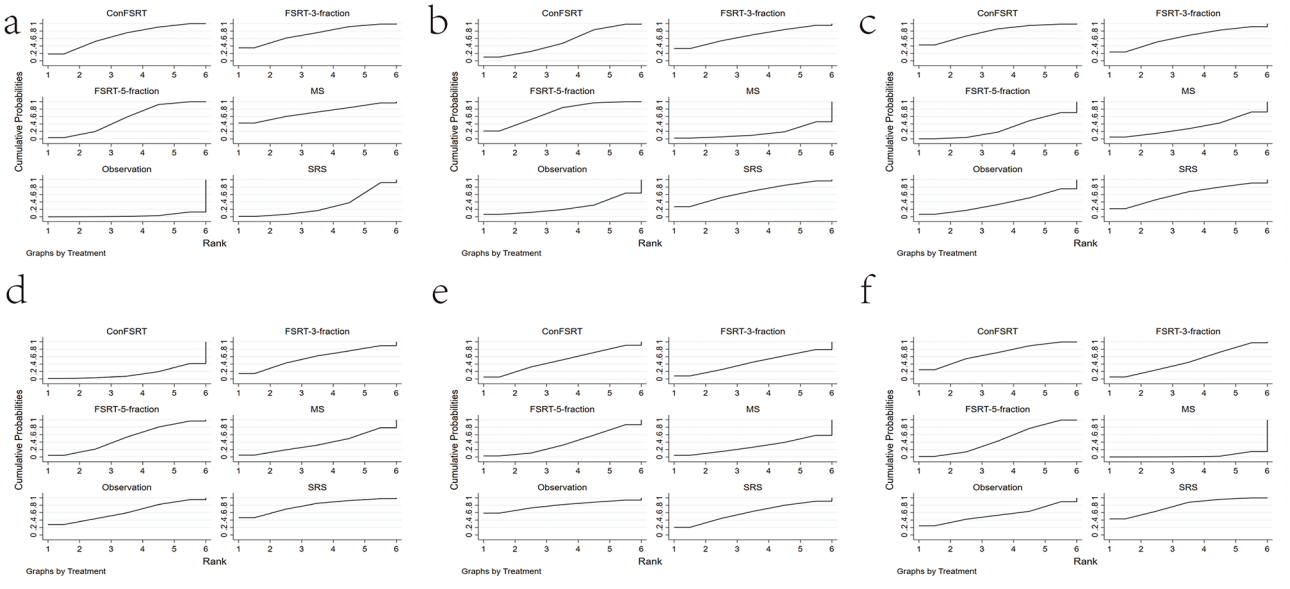

Fig. 3 The Rank Chart, **a**: The rank chart based on the local control tumor rates in patients with VS, **b**. The rank chart based on the preserved hearing in patients with VS, **c**. The rank chart based on the improved tinnitus in patients with VS, **d**. The rank chart based on the improved disequilibrium/vertigo in patients with VS, **e**. The rank chart based on the reduced trigeminal nerve toxicity in patients with VS, **f**. The rank chart based on the reduced facial nerve toxicity in patients with VS

tumor growth and, owing to its advantages, and makes the increase in the number of patients treated by this intervention. However, the efficacy of these interventions in terms of tumor control and function preservation is uneven.

In this study, we performed a traditional meta-analysis for a preliminary exploration of tumor control and neurological protection of VS patients after different interventions. Considering that VS is a benign tumor, many researchers and patients choose to have regular examinations (i.e., observation treatment) in the early stage of the disease, which is the basic treatment strategy for VS [46]. In this study, traditional meta-analysis was used to explore the benefits of MS, ConFSRT, and SRS in comparison with observation treatment. Although tinnitus and disequilibrium/vertigo were not improved in the MS group, the rate of preserved hearing was better than that in observation treatment. Compared with the observation treatment, there was no significant difference between ConFSRT and SRS in terms of preservation of hearing, tinnitus, and trigeminal and facial nerve toxicity, however, it has a better rate of tumor local control. This is consistent with the findings of Dhayalan D, et al., [16] and Leon J, et al., [47], who pointed out that ConFSRT and SRS have benefits in the local tumor control rate but have no significant benefits in improving vestibular function (such as vertigo and tinnitus) and neuroprotection. Therefore, the choice of immediate removal of the tumor or regular examination for the early detection of the lesion remains to be discussed.

Surgery is the most common treatment for VS. With developments in microsurgical technology, the operating microscope has been used for VS. Thus, surgery in these patients not only prevents death, but also allows the complete resection of tumors while preserving hearing and facial nerve function [48, 49]. Moreover, SRS is among the optional methods for surgical treatment of VS. Therefore, in this study, we used a traditional meta-analysis to explore the efficacy of SRS and MS. We found no significant difference in the aspects of tumor local control, preserved hearing, tinnitus, disequilibrium/vertigo, and trigeminal nerve toxicity, however, but the incidence of facial nerve toxicity was reduced. Similar to the results of a meta-analysis conducted by Jakubeit et al., [3] compared with MS, SRS improved not only facial nerve toxicity, but also trigeminal nerve toxicity. This difference may be attributed to the low sample size of this study. Therefore, the apparent trigeminal nerve toxicity associated with MS and SRS requires further exploration.

Subsequently, in this study, compared with FSRT 5 fractions, FSRT 3 fractions, and ConFSRT, SRS showed no significant association between local tumor control rate, preserved hearing, tinnitus, disequilibrium/vertigo, trigeminal nerve toxicity, and facial nerve toxicity. This is consistent with the findings of Söderlund Diaz et al., [41] who found that SRS, FSRT 3 fractions, and FSRT 5 fractions had no significant differences in improving the rate of tumor local control, preserved hearing, trigeminal nerve toxicity, facial nerve toxicity, tinnitus, and disequilibrium/vertigo.

In addition, we explored the effects of ConFSRT and FSRT 5 fractions on tumor control and the protection of neural and vestibular function. There were no statistically significant differences between the two interventions in these aspects. Similar to the results of Anderson BM, et al., [8] we confirmed that ConFSRT and FSRT 5 fractions had comparable efficacy in terms of tumor control, neuroprotection, and vestibular function protection, with no statistically significant differences. Slane BG, et al. [40] found that both interventions had similar good local tumor control rates and minimal toxicity, however, they suggested that FSRT 5 fractions are more convenient for patients to treat and may, therefore, be more suitable.

Considering that traditional meta-analysis is based on the pairwise direct comparison of effect sizes, data for direct comparison are relatively limited [50]. Nevertheless, there is a growing need for indirect comparisons between different treatment interventions with the same efficacy used in clinical practice [51, 52]. This network meta-analysis includes allowed both direct comparisons and indirect comparisons based on logical reasoning.

To the best of our knowledge, this study was the first attempt at a network meta-analysis for a comprehensive analysis of direct and indirect comparative evidence for the three major treatment interventions for VS. We found that the rate of tumor local control was better with surgery and radiotherapy than with observation treatment, with MS, FSRT 3 fractions, and ConFSRT having the best tumor local control rate. In terms of preserved hearing, radiotherapy had a better rate than observation treatment and MS, and the best radiotherapy protocol was FSRT 5 fractions, FSRT 3 fractions, and SRS in this order. In terms of neuroprotection, various radiotherapy protocols have better neuroprotection than MS, and SRS was the best intervention. In terms of improvement of vestibular function (i.e., disequilibrium and vertigo) and tinnitus, radiotherapy intervention also had a good effect.

This study had some limitations. First, most of the included studies were non-randomized controlled trials, which reduced the strength of evidence in our analysis to some extent. Therefore, high-quality, large-scale, multicenter RCTs are required to further verify the efficacy and safety of the current treatment options, including observation, microsurgery, and radiotherapy, for VS. Second, the radiotherapy methods included in this study were GammaKnife, CyberKnife, and linear accelerator, which were not divided in detail according to specific radiotherapy methods in our analysis. Thus, whether

different radiotherapy methods affect the outcome of patients should be explored. We plan to address these limitations in our follow-up study.

Conclusion

This network meta-analysis indicated that in patients with VS, MS, FSRT 3 fractions, ConFSRT, FSRT 5 fractions, and SRS showed better local tumor control rates, however, compared with MS, FSRT 3 fractions, FSRT 5 fractions, SRS, and ConFSRT were associated with better protection of nerve function and improved symptoms of vestibular function and tinnitus, among which the best one was SRS. Therefore, in patients with unilateral VS, SRS may be a promising alternative treatment. However, there are only a few high-quality randomized controlled clinical trials on MS, different SRS, and observation, thus, the feasibility of SRS for clinical practice requires further exploration.

Abbreviations

VS	Vestibular schwannoma
MS	Microsurgery
SRS	Stereotactic radiosurgery
FRST	Fractionated stereotactic radiotherapy
GKS	Gamma knife surgery
CM	Conservative management
NOS	Newcastle–Ottawa Scale
ConFSRT	Conventionally-fractionated stereotactic radiotherapy; y
NR	Not report
LC	Local control
RCT	Randomized controlled trial

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Author contributions

L.M. and H.X.H. performed the study subject and design, data extraction, statistical analysis, interpretation of data and manuscript drafting T.J.H., L.M., and H.X.H. contributed to the study design, statistical analysis and manuscript revising Z.X. contributed to the study design, interpretation of data L.X.Z. performed statistical analysis Z.Y.F. and H.X.H. extracted the data. L.M. and T.J.H. performed quality assessment H.X.H. and Z.X. was involved in critical revision of manuscript.

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Data availability

Data is provided within the manuscript.

Declarations

Ethics approval and consent to participate

Not Applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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