Primary Treatment of Small-To-Medium (<3cm) Sporadic Vestibular Schwannomas: A Systematic Review And Meta-Analysis on Long-Term Hearing Preservation And Tumor Control Rates For Microsurgery Versus Radiosurgery.

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Abstract

Background

Over the past two decades, the treatment of small-to-medium (<3cm) sporadic vestibular schwannomas (VS) has experienced a definite shift to stereotactic radiosurgery vis-a-vis microsurgery. We performed a systematic review and meta-analysis of VS patients primarily treated with stereotactic radiosurgery (SRS) or microsurgery (MS), with particular attention to hearing preservation outcomes (HPO), tumor control (TC), and facial nerve dysfunction (FND).

Methods

A systematic review was conducted (Medline and Scopus database) for the period, January 2010 to June 2020 with appropriate MeSH. English language articles for small-to-medium sporadic VS (<3cm) utilizing SRS or MS as treatment modality, with minimum follow-up of 3 years, were included. Studies had to report an acceptable standardized hearing metric. HPO, TC, and FND rates were analyzed.

Results

Thirty-two studies met inclusion criteria: 10 for microsurgery; 23 for radiosurgery (one comparative study included in both). HPO, at ~65 months follow-up, were comparable between MS group (10 studies; 809 patients) and SRS group (23 studies; 1234 patients) (56% versus 59%, $p=0.1527$). TC, at ~70 months follow-up, was significantly better in MS group (9 studies; 1635 patients) versus SRS group (19 studies; 2260 patients) (98% versus 92%, $p < 0.0001$). FND, at ~12 months follow-up, was significantly higher in MS group (8 studies; 1101 patients) versus SRS group (17 studies; 2285 patients) (10% versus 2%, $p < 0.0001$).

Conclusion

MS and SRS are comparable primary treatment options for small (<3cm) sporadic VS with respect to HPO at 5-year follow-up in patients with serviceable hearing at presentation. Approximately 50% patients for both modalities will likely lose serviceable hearing by that time-point. High TC rates (>90%) were seen with both modalities, with MS (98%) significantly better than SRS (92%). The post-treatment FND was significantly less with SRS group (2%) versus MS group (10%).

Introduction

Vestibular schwannomas (VS) are benign neoplasms arising from the nerve sheath (Schwann cells) of the vestibulocochlear nerve.[21] The last 100 years have seen a significant change in treatment outcomes for VS with the goal shifting from disease eradication to function (facial and hearing) preservation;[6] this is particularly true for small-to-medium VS (< 3cm) with serviceable hearing and without signs and symptoms of brainstem compression.[27] The three options for patients with small-to-medium VS treatment are: observation, stereotactic radiosurgery (SRS) and microsurgery (MS); with SRS and MS being the two primary treatment modalities.[6, 9] Our objective was to conduct a meta-analysis of previously published recent literature (2010 to 2020) comparing long-term outcomes for SRS and MS for small-to-medium VS (< 3cm) with regards to hearing preservation outcome (HPO), tumor control (TC), and post-treatment facial nerve dysfunction (FND).

Methods

Literature search strategy

A systematic review was conducted to analyze long-term treatment outcomes for SRS and MS for small-to-medium VS (< 3cm) with regards to tumor control, useful hearing preservation and post-treatment cranial neuropathies. The search strategy was designed around the PICOTS question format: Do patients with small-to-medium sporadic VS (< 3cm) [Population] treated primarily with SRS [Intervention] compared to MS [Comparison] differ in tumor control and functional (facial nerve function and useful hearing preservation) outcomes [Outcome] at long-term follow-up (Mean/Median follow-up period > 3 years) [Time] as reported in recently published (last decade) observational studies [Study design].[33, 12] To focus on contemporary data and provide a snapshot of current trends in treatment outcomes, the literature search was restricted to clinical articles in English language dealing with human subjects in the last 10 years. We adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[29]

In the first step two investigators (SJL and PRK) independently searched titles and abstracts in databases with appropriate keyword queries. In the second step, two different reviewers (ARS and DLT) independently evaluated the selected abstracts from Step 1 (full text articles if necessary) vis-a-vis the inclusion criteria to identify studies for inclusion, which were then scrutinized in full-text format. The reference lists of identified studies, reviews and meta-analyses were also searched for other relevant articles. The process is detailed in Fig. 1.

Inclusion and exclusion criteria

Inclusion criteria:

- 1) Full text English language articles published in the last 10 years [Jan 2010 to July 2020] on the treatment of sporadic VS;
- 2) VS tumor size less than 3cm [mean largest diameter] or 15.6 cm³ [mean volume]; studies reporting on tumor sizes more than 3cm (largest diameter) were excluded.

3) SRS or MS utilized as primary treatment for VS;

4) Follow-up length clearly stated and ≥ 3 years (median or mean);

5) Pre- and post-treatment hearing outcomes clearly documented using the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS), Gardner-Robertson (GR), or an audiogram-based hearing scale (using the 50/50 rule – PTA threshold < 50 and SDS $> 50\%$). [14, 30]

Exclusion criteria:

1) Duplicate data sets

2) Studies with NF-2 patients included

3) Studies with previously treated (surgery or radiation) VS patients included

4) Data loss at follow-up $> 50\%$

5) Case reports or case series < 10 patients

Data Extraction

The full text articles were mined for the following data: Information on study design (prospective, retrospective, mono- or multi-center and follow-up duration), patients (age, sex and number of patients), lesion characteristics (grading, number, volume and/or diameter, site), surgical approach, radiation treatment (type of SRS, dose, number of fractions, treatment volume) and results – HPO, TC, FND (point estimates and confidence interval for outcome data). If further information was deemed necessary, the authors were directly contacted.

Type of interventions

The treatment modalities analyzed included microsurgery (MS) and stereotactic radiosurgery (SRS). The MS approaches included the two hearing preservation approaches – middle cranial fossa (MCF) approach and the retro-sigmoid (RS) approach. SRS included modalities delivering a high total dose of radiation [≥ 12 Gy (as per current standards)[23]] to the tumor in a single fraction with a dedicated device, such as Gamma Knife, LINAC and Cyberknife systems.

Outcome Measures

The primary outcomes analyzed were:

1) Hearing preservation outcomes (HPO): HPO was defined as preservation/retention of 'serviceable' hearing post-treatment and at last available audiological follow-up, in those patients who had pre-treatment serviceable hearing in the affected ear. Serviceable hearing was defined as pure tone average < 50 dB and speech discrimination $> 50\%$. This corresponded to patients who either had AAO-HNS grade A or B, or G-R grade 1 or 2.[14]

2) Tumor control (TC): Failure of TC was defined as 'recurrence of tumor after total resection' in the MS group or 'increase in tumor volume of $> 10\%$ as compared to pre-treatment volume for either group' or 'need for salvage therapy'. Tumor pseudo-progression or transient increase in tumor volume after SRS was not considered as failure. Actuarial disease control rates or actuarial progression free survival rates were not considered.

3) Facial Nerve Dysfunction (FND): New-onset or worsening of facial neuropathy was studied as this aspect has been significantly linked to post-treatment QoL scores.[16] FND was defined as any new-onset or worsening of post-intervention facial function to H-B grade 3 or higher. FND rates noted by studies at early clinic follow-up (6 weeks to 1 year) were considered.

Statistical analysis

All data regarding patient demographics and clinical measures from reviewed studies were tabulated in Microsoft Excel (Redmond, Washington), Data was then transferred into R (Vienna, Austria) for further analyses. Aggregate rates for each outcome and corresponding confidence intervals (CIs) were estimated using both fixed-effects model as well as random-effects model; however, the fixed-effect model was considered (considering the homogenous patient population of small-to-medium, sporadic vestibular schwannomas) while comparing SRS versus MS for each outcome via z-test. P -values less than 0.05 ($P < 0.05$) were considered significant. Study heterogeneity was quantified using I^2 statistics. Study bias was assessed using standard funnel plot generation and representation. All analyses were run in the software R (Foundation for Statistical Computing, Vienna, Austria).

Results

PubMed search and Eligibility screening

The Medline and Embase search identified 1024 records. Out of these, 913 citations were discarded following abstract review in view of duplicates, irrelevance to the study objective, nature of publication (review articles, editorials, letter to editor, case reports) and non-availability of original data. The full text of the remaining 111 papers were examined in detail and further 79 publications were eliminated in adherence to the inclusion criteria. The reasons for exclusion for each publication are reported in Supplementary Table 1. Thirty-two studies, thus, were eligible for data extraction and analysis. The 10 studies selected for MS for small VS are detailed in Table 1.[1, 10, 16, 19, 35, 43, 46, 47, 49, 50] The 23 studies selected for the SRS for small VS are detailed in Table 2.[5, 32, 17, 36, 42, 48, 38, 44, 3, 26, 8, 22, 16, 20, 25, 45, 4, 28, 31, 37, 7, 18, 11] One study was a matched cohort comparison and was included in both arms.[16]

Table 1
List of excluded publications with reasons for exclusion

Author, Publication Year	Enrollment Period	Type of study		Patient's analyzed		Age (years)	F/U (months)	Approach	Mean Tumor Size
		Center	Design	N	Males (%)	Mean/Median (range)	Mean/Median (range)		(mm)
Hilton et al., 2010	Dec 89 to Dec 09	Single	Retrospective	87	52.7	45 (23–76)	48	MCF	12
Woodson et al., 2010	1993 to 2004	Single	Retrospective	49	61	48 (19–69)	70.5	MCF	N/A
Vincent et al, 2012	1995 to 2006	Single	Retrospective	77	N/A	49 (33–68)	102	MCF	9
Yamakami et al, 2014	1998 to 2012	Single	Retrospective	44	43.18	52+/-12 (22–69)	81 ± 43	RS	<= 15mm
Quist et al, 2015	Feb 98 to Dec 09	Single	Retrospective	57	N/A	47.65 +/- 15.11 (27–90)	60	MCF	N/A
Golfinos et al, 2016 (MS Group)	2001 to 2014	Single	Retrospective (matched- cohort)	85	45.9	58.0 (27.9–71.6)	HPO – 43.7; FND – 35.7	MCF and RSA	12.2 (median)
Zhang et al., 2016	Jan 1990 to Dec 2006	Single	Retrospective	1006	46.91	55.6 +/- 13.6	70.8+/-28.8	TL, TO, RS, MCF	17.2 (+/- 11.7)
Ahmed et al.,2017	1999 to 2016	Single	Retrospective	155	N/A	49	84	MCF	9.3
Zhu et al, 2017	Jan 2001 to Dec 2015	Single	Retrospective	110	51.81	43.2+/- 13.1 (23–70)	49.1+/- 28.2	RS	Max diameter <= 15mm
Dowling et al., 2019	2003 to 2016	Single	Retrospective	43	40	45 (median) (21–64)	37	RS or MCF	9

Table 2
Outcomes data for MS Group Studies

Author, Publication Year	Enrollment Period	Type of study		Patient's analyzed		Age (years)	F/U (months)	Type of SRS	Tumor size	Prescribed Dose
		Center	Design	N	Males (%)	Mean/Median (range)	Mean/Median (range)		Volume (cc)/Max Diameter(cm)	
Park, 2011 (GKRS group)	Jan 2004 to June 2009	Single	Retrospective	31	45.2	59.7 +/- 10.8	43.8 +/- 22.3	GKRS	1.93 +/- 7.05	Maximal dose – 24.4, Marginal dose – 14.2
Han, 2012	1998 to 2009	Single	Retrospective	119	37.8	48 +/- 11	55.2 +/- 35.7	GKRS	1.95+/- 2.24cm3	Mean marginal dose – 12 Gy
Roos, 2012	Nov 1993 to Dec 2000	Single	Prospective	44	59.1	63 (33 to 75)	128	LINAC	2.1cm	14 Gy (n = 4); 12 Gy (n = 40)
Varughese, 2012	2000 to 2007	Single	Prospective	45	57.8	53.2 (R – 29 to 77.3)	50 (23.8 to 86.7)	GKRS	1.05cc	Mean maximum dose – 32.6 Gy
Yomo, 2012	July 1997 to Sept 2005	Single	Retrospective	154	50	54.1 (R – 24 to 78)	60 (7 to 123)	GKRS	0.73cc (R – 0.03 to 5.37))	12.1 Gy
Carlson, 2013	1997 to 2002	Single	Retrospective	44	52	56.9 +/- 8.9	99.6	GKRS	1.698+/-2.814cc	12-13Gy
Sager, 2013	July 1998 to Jan 2013	Single	Retrospective	51	41.2	45 (R – 20 to 77)	51 (median)	LINAC	1.83cm	12Gy(median)
Vivas, 2013	Aug 2005 to Nov 2011	Single	Retrospective	63	44	59 (R – 23 to 86)	40 (R – 6 to 81)	Cyberknife	0.81cc	18Gy(80% of isodose line)
Boari, 2014	2001 to 2010	Single	Retrospective	379	43	59 (R – 23 to 85)	75.7	GKRS	1.94 ± 2.2 cm3 Median 1.2 cm3 (0.013–14.3)	Maximum dose – 20-32.6(26), Marginal dose – 11–15(13)
Carratalá, 2014	Jan 1999 to Jan 2010	Single	Retrospective	35	49	58.3 (R – 31 to 76)	56.39	GKRS = 29; LINAC = 6	1.517	12–13
Combs SE, 2015	1990 to 2012	Multi	Retrospective	169	55	60 (R – 17 to 88)	67 (R – 2 to 252)	LINAC	1.5cm	For SRS, median dose was 13 Gy (range 10–20 Gy).
Ikonomidis, 2015	Jan 2002 to Aug 2010	Single	Retrospective	151	49	55 (R – 22 to 81)	39 (R – 6 to 84)	LINAC	NA	12Gy
Golfinos, 2016 (SRS Group)	2001 to 2014	Single	Retrospective (matched - cohort)	83	48.2	59.0 (R – 32 to 75)		SRS	HPO – 1 cm; FND – 1.2 cm; TC – 1.2 cm	12–13
Horiba, 2016	Jan 2005 to Sept 2010	Single	Retrospective	102	N/A	N/A	56 (R – 24 to 99)	GKRS	NA	Mean marginal dose-11.9 Gy(11-12Gy)
Klijn, 2016	July 2002 to Nov 2010	Single	Retrospective	420	52	57.6 +/- 12.7	61.2 (R – 2 to 144)	GKRS	1.4 cc (0.01 to 17.7)	median marginal dose – 11Gy
Watanbe, 2016	1990 to 2005	Single	Retrospective	183	45	56 (R – 11 to 80)	Imaging – 114; audiological – 59	GKRS	2.0cc (R – 0.05 to 26.2)	12Gy at the periphery, 10 Gy at the facial and cochlear part
Bowden, 2017	Jan 2003 to Dec 2013	Single	Retrospective	219	50.2	55.7 (R – 23 to 99)	49.1	GKRS	1.9 cm(diameter), 2.6 cm3(volume)	12.5 (11–13)

Author, Publication Year	Enrollment Period	Type of study		Patient's analyzed		Age (years)	F/U (months)	Type of SRS	Tumor size	Prescribed Dose
Milner, 2017	2000 to 2012	Single	Retrospective	45	45	55.8 (R - 34 to 75)	69.6	GKRS	1.75cc	12-13
Pan, 2017	July 2003 to Dec 2008	Single	Retrospective	93	64.5	57.7 (+/- 15.1)	76.3 ± 3.6	GKRS	3.14 ± 0.05 cc	12 Gy
ReuB, 2017	1993 to 2015	Single	Retrospective	49	57.2	54 (R - 20 to 77)	65	LINAC = 38; Cyberknife = 11	0.24 ± 0.12 cc	12.6+/-0.6 Gy
Chung, 2018	May 2009 to Nov 2014	Single	Retrospective	38	35.7	65.3 (40.2 to 79.4)	38.3 (R - 13.3 to 67.5)	LINAC	2.13cc	12 Gy
Hasegawa, 2018	May 1991 to Dec 2013	Single	Retrospective	92	41	54 (R - 17 to 77)	Imaging - 106; audiological - 83	GKRS	1.5cc	12 Gy
Dzierzecki, 2020	2011 to 2015	Single	Retrospective	136	40.4	54 +/- 12.6	Imaging - 54; audiological - 41	GKRS	0.155cc (volume)	12 Gy, mean cochlear dosing - 2.3 Gy

Study characteristics

Eligible studies were published between 2010 and 2020 (as per inclusion criterion) and reported on patients treated within the period 1989 to 2016. All studies were observational and retrospective in design, except for 2 studies in SRS group which had prospective databases.[36, 42] Cases per study ranged from 43 to 1006 for the 10 studies in the MS group, with a mean of 171 patients/study and median of 71 patients. Cases per study ranged from 31 to 420 for the 23 studies in the SRS group, with a mean of 119 patients/study and median of 92 patients. In the MS group, patients were treated exclusively by the MCF approach in 5 studies:[19, 46, 43, 35, 1] exclusively by the RS approach in 2 studies:[50, 47] and by either of the two approaches (MCF or RS) in 3 studies.[16, 49, 10] In the SRS group, patients were treated exclusively with GKRS in 14 studies:[32, 17, 42, 48, 5, 3, 20, 25, 45, 4, 28, 31, 18, 11] exclusively with LINAC in 6 studies:[36, 38, 8, 22, 7, 26] exclusively with Cyberknife in 1 study:[44] with LINAC or Cyberknife in 1 study:[37] and one study did not specify the source of the SRS.[16]

Patient and Tumor characteristics

The total number of patients analyzed were 4,458; 1,713 for the MS group and 2,745 for the SRS group. The average age of patients at primary treatment ranged from 43.2 to 58 years (mean: 49.25 +/- 4.73 years) for the MS group; and from 45 to 63 (mean: 55.92 +/- 3.95 years) for the SRS group. The mean age of the MS group was significantly lower than that of the SRS group ($p = 0.0002$). In terms of gender composition, the percentage of males in the study cohorts ranged from 40 to 61 % (m: 48.79%) for the MS group and from 35.7-64.5% (m: 48.29%) for the SRS group ($p = 0.8758$). The overall mean follow-up period was 64.67 (± 20.64) months for the MS group and 66.15 (± 24.91) months for the SRS group ($p = 0.8715$). Table 1 and Table 2 summarize the study characteristics, patient demographic and clinical variables for patient cohorts across the 10 studies analyzed for the MS outcomes and the 23 studies analyzed for the SRS outcomes, respectively. Study outcomes are detailed in Supplementary Tables 2 and 3.

Hearing Preservation Outcome – MS versus SRS (Fig. 2)

For the MS group, 10 studies with 809 eligible patients were analyzed for HPO. Serviceable HPO was noted in 56% (CI: 52 to 59%) of cases/patient-events with a mean follow-up of 64.6 months. For the SRS group, 23 studies with 1234 eligible patients were analyzed for HPO. Serviceable HPO was noted in 59% (CI: 56 to 62%) of cases/patient-events with a mean follow-up of 66.2 months. Overall, serviceable HPO rates were noted as 56% and 59% for MS group and SRS group, respectively [p (z-test) = 0.1527] and the difference was statistically non-significant.

Tumor Control Outcome – MS versus SRS (Fig. 3)

For the MS group, 9 studies with 1635 eligible patients were analyzed for TC. TC was seen in 98% (CI: 97 to 98%) of cases with a mean follow-up of 69.8 months. For the SRS group, 19 studies with 2260 eligible patients were analyzed for TC. TC was seen in 92% (CI: 91 to 93%) of cases with a mean follow-up of 74.2 months. Overall, TC was reported in 98% and 92% of MS group patients and SRS group patients, respectively [p (z-test) < 0.0001] and the difference was statistically significant.

Facial Nerve Dysfunction – MS versus SRS (Fig. 4)

For the MS group, 8 studies with 1101 eligible patients were analyzed for FND (new onset or worsening facial nerve dysfunction $\geq$ H & B grade 3) and FND was reported in 10% (CI: 8 to 12%) of cases. For the SRS group, 17 studies with 2285 eligible patients were analyzed for FND, which was reported in 2% (CI: 1-2%) of cases. Overall, FND rates were 10% and 2% for MS group and SRS group, respectively [p (z-test) < 0.0001] and the difference was statistically significant. For the FND outcome, there was significant heterogeneity noted for the studies in the MS arm. Amongst the outliers, the study by Zhang et al., reported FND rates of 13.6% (80 events in 585 patients);[49] while the studies by Woodson et al., Yamakami et al., and Dowling et al., reported 0, 0, and 1 event in 49, 44 and 43 patients respectively.[46, 47, 10] The studies in the SRS arm did not exhibit significant heterogeneity with respect to the FND outcome.

Discussion

Over the last two decades, there has been a paradigm shift in the treatment of small (< 3cm), sporadic VS with SRS emerging as the primary treatment modality.[13] In addition to facial nerve outcomes and TC, HPO is gaining traction as an outcome measure for small-to-medium VS.[27, 9, 14] Currently, there is no consensus on the 'gold standard' treatment for newly diagnosed small-to-medium, sporadic VS.

Hearing Preservation Outcomes

In 2000, Kaylie et al., published a meta-analysis comparing MS versus GKRS for VS (up to 4cm in size) and reported HPO rates of 44% in both groups (with no statistical difference) with an overall mean follow-up of 2.03 years.[24] In contrast, Maniakas et al., (2012) published a meta-analysis on MS versus SRS for VS (size < 2cm) with more than 5 years of follow-up and reported significantly higher HPO rates for SRS group (70.2%) versus MS group (50.3%) [$p < 0.001$]. [27] More recently, in a systematic review on hearing preservation after primary radiotherapy for VS, Coughlin et al. (2018) found long term HPO to be 58% at an average reporting time of 46.6 months.[9] There was strong evidence for progressive hearing loss as the time to follow-up extended to 10 years. The same group (Hunt and Coughlin) performed a systematic review on hearing preservation rates after MS resection of VS and reported an HPO rate of 57% at mean follow-up of 52.5 months;[21] noting that when hearing was preserved in the immediate (MS) post-operative period, it seemed to be stable over time. In a systematic review of 26 studies ($n = 2034$) reporting HPO for surgically resected VS via the RS approach, Preet et al. (2020) using a generalized linear mixed model, postulated that HPO rates were dependent on preoperative tumor size, with rates of 57%, 37%, and 12% observed for intra-canalicular, small, and large (> 20 mm) tumors, respectively.[34] In a large single institution study comprising 326 patients with preserved serviceable hearing (pre-treatment), Johnson et al., report HPO rates of 68.4% at 5 years and 51.4% at 10 years for GKRS.[23] Our results [HPO – 56% for the MS group (overall mean f/u – 64 months) and 59% for the SRS group (overall mean f/u – 66 months)] show that MS and SRS are comparable ($p = 0.1527$); however, ~ 50% patients are likely to lose serviceable hearing at 5-year follow-up irrespective of the primary treatment modality chosen. This is in line with the evidence-based CNS guidelines on HPO in patients with sporadic VS.[6]

Tumor Control Outcomes

Both MS and SRS have been shown to produce excellent tumor control for VS. Recent literature for MS reports tumor recurrence in only 0.5 to 5% of operated cases at long-term follow-up;[27] while for SRS, tumor control rates of 89–96% have been reported.[27, 2, 23] In a large single institution study comprising 871 VS patients treated with Gamma Knife radiosurgery, Johnson et al. reported tumor growth control in 94% of patients at 10 year follow-up.[23] In the meta-analysis by Kaylie et al. (follow-up period: 2.05 years), published in 2000, MS was shown to have significantly better recurrence-free rate (98.5%) as compared to the SRS group (91%). [24] In the meta-analysis by Maniakas et al., (follow-up period: 8.16 years), recurrence was seen in 1.3% cases in the MS group whereas tumor control was seen in 96.2% and both groups were comparable.[27] Our results echo those of previous studies, with excellent tumor control rates in both groups; however, they are most in line with those of Kaylie et al., in that MS TC rates (98%) were better (statistically significant) than SRS TC (92%) rates. This is also in accordance with the traditional thought that MS offers better overall tumor control for schwannomas.[39, 41]

Complications and Facial Nerve Function Outcomes

Traditionally, FND rates for microsurgical series for VS have ranged from 0 to 23% (with tumor size being a significant factor); while those for SRS have ranged from 0 to 4.8%.[27] In a frequently cited MS series by Samii et al., on 1000 VS patients (all tumor sizes), overall complications were seen in ~ 15 patients and facial nerve preservation was seen in 93% cases.[41, 15, 40] In the meta-analysis by Maniakas et al., long-term facial neuropathy rates after MS ranged from 0 to 5.3%.[27] Our analysis considered FND rates at early clinic follow-up, and the results clearly favored SRS over MS (10% versus 2%, respectively). Based on available data and our group's experience, it is very likely that restoration of facial nerve function towards normal would be seen if long-term follow up (6 months or greater) was available (assuming that the facial nerve was anatomically intact with low threshold positive intraoperative stimulation at the end of surgery).

Limitations of the study

All included studies contained some limitations; all except two were retrospective and all except one were non-comparative. The power of our sub-group analysis is somewhat diluted as analysis was carried out using averages of each study since individual patient data-points were not available. A common data-point which required grouping was follow-up period. This may have been either clinical, radiographic, or audiometric follow-up but was not often specified or broken down for audiometric only; when not otherwise specified, audiometric follow-up was assumed to be the same as overall follow-up.

One potential bias for the SRS group is that patients are older (which was confirmed in our analysis). Groups with older age may have more hearing loss during the same follow-up period. For the SRS group, three SRS studies seemed to use higher dose (the standard SRS marginal dose is typically 12-13Gy).[44, 32, 8] If the study used marginal dose > 13Gy or maximal dose > 26Gy, it may reduce HPO rate. Since each study typically reported mean or median dose, individual patients receiving higher than standard dose may have influenced HPO. SRS research shows better HPO when keeping the cochlea dose < 4-8Gy. The closer the tumor is to the cochlea, the harder it is to abide by this constrain. In most studies, the distance or actual dose to the cochlea was not reported and we were unable to analyze this variable. For the MS arm, one study (Zhang et al., 2016) had 1006 (59% of the total included) patients which may have over-powered the analysis while considering TC and FND rates; however, only 245 patients had serviceable pre-treatment hearing and hence the meta-analysis for HPO was considered balanced.[49]

Conclusion

MS and SRS are comparable primary treatment options for small (< 3cm) sporadic VS with respect to HPO at 5-year follow-up in patients with serviceable hearing at presentation. Approximately 50% patients for both modalities will likely lose serviceable hearing by that time-point. High TC rates (> 90%) were seen

with both modalities, with MS (98%) significantly better than SRS (92%). The post-treatment FND was significantly less with SRS group (2%) versus MS group (10%).

Declarations

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Conflicts of interest/Competing interests: None; no disclosures.

Availability of data and material (data transparency): All data related to the project is available in the supplementary file.

Code availability (software application or custom code): Not applicable.

Ethics approval (include appropriate approvals or waivers): Not applicable; no data was used from our institution since this was a systematic review and meta-analysis.

Consent to participate (include appropriate statements): Not applicable.

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Authors' contributions:

Conception and design: Savardekar, Kosty, Guthikonda

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Figures

Figure 1

Literature search strategy for the systematic review and process of selection of final articles is detailed as per PRISMA guidelines.

Figure 2

(A) Forest Plot for HPO in the MS group; (B) Funnel plot for HPO in the MS group; (C) Forest Plot for HPO in the SRS group; (D) Funnel plot for HPO in the SRS group.

Figure 3

(A) Forest Plot for TC in the MS group; (B) Funnel plot for TC in the MS group; (C) Forest Plot for TC in the SRS group; (D) Funnel plot for TC in the SRS group.

Figure 4

(A) Forest Plot for FND in the MS group; (B) Funnel plot for FND in the MS group; (C) Forest Plot for FND in the SRS group; (D) Funnel plot for FND in the SRS group.

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