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Key Words: Hearing; Stereotactic radiosurgery; Neurofibromatosis type 2; Vestibular schwannoma

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Abstract

Objective: Neurofibromatosis type 2 (NF2) is an autosomal dominant disease characterized by bilateral vestibular schwannomas (VS). NF2-associated VS (NF2-VS) are routinely treated with microsurgery; however, stereotactic radiosurgery (SRS) has emerged as an effective alternative in recent decades. To better elucidate the role of SRS in NF2-VS, a systematic review of the literature was conducted to compare outcomes of SRS versus surgery.

Methods: PubMed, Web of Science, Scopus, Embase, and Cochrane databases were queried using relevant search terms. Retrospective studies investigating outcomes of NF2-VS patients treated with either SRS or surgery were included. Single patient case reports were excluded. Outcome measures between the SRS and surgery groups were compared using chi-square two-sample tests for equality of proportions on the pooled patient data.

Results: A total of 974 patients (485 SRS, 489 surgery) were identified. The mean 5-year local control rate for SRS was 77.6% and the mean recurrence rate for surgery was 5.3%. The mean hearing and facial nerve preservation rates were 37.5% and 89.5%, respectively, for SRS and 46.9% and 69.9%, respectively, for surgery. Rates of hearing preservation were higher after surgery than SRS (p = 0.006), while rates of facial nerve preservation were higher after SRS than surgery (p < 0.001).

Conclusions: SRS appears to be a safe and effective alternative to surgery for NF2-VS. Although rates of hearing preservation were higher in the surgery cohorts, SRS demonstrated high rates of
local control and significantly lower facial nerve complications. Certain patients may therefore benefit more from SRS than surgery.

**Key Words:** Hearing; Stereotactic radiosurgery; Neurofibromatosis type 2; Vestibular schwannoma
Introduction

Neurofibromatosis type 2 (NF2) is an autosomal dominant disease characterized by multiple neoplasms due to a mutation in the tumor suppressor gene \( \text{NF2} \) on chromosome 22q12 [1-3]. NF2 prevalence is estimated at 1 in 25,000 live births and may present with a variety of symptoms [4, 5]. Individuals with NF2 often develop multiple neoplasms in the skin, eyes and central nervous system [1, 2, 6]. By the age of 60, the disease has nearly 100% penetrance [2, 6].

Bilateral vestibular schwannomas (VS) are the hallmark of the disease.

NF2-associated VS (NF2-VS) are most frequently managed through conservative means with annual magnetic resonance imaging scans to monitor for disease progression [7-9]. When intervention is indicated, VS are routinely treated with microsurgery for tumor resection. Although complete resection may be curative, the multilobulated morphology and infiltrative nature of the tumor induces significant risk for iatrogenic injuries during surgery, namely hearing loss and facial nerve damage [10]. Advancements in microsurgical techniques have reduced the risk of complications to adjacent cranial nerves, but hearing loss remains relatively high despite these new developments [11].

More recently, stereotactic radiosurgery (SRS) has been successfully used to mitigate many of the risks associated with surgery [12-20]. In most experienced centers, SRS now achieves long-term tumor control in more than 95% of sporadic VS cases [21-23]. This lends credence for SRS as a primary treatment modality for NF2-VS [24, 25]. Although SRS has demonstrated high local control rates in NF2-VS, one concern with radiation is the potential for malignant tumor
transformation. As a result, controversy remains among clinicians regarding the use of SRS as a treatment option. In this study, the authors systematically analyzed the current literature to examine outcomes of SRS versus surgery for the treatment of NF2-VS.

Methods

Adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was maintained throughout the preparation of this study.

Sources and Search Strategy

A systemic review of the literature was performed by independent authors (LC and TN) to identify studies that investigated outcomes of SRS and surgery for NF2-associated VS. A search was conducted through PubMed, Web of Science, Scopus, Embase, and Cochrane databases in November 2016 using a strategic combination of terms: “neurofibromatosis type 2,” “vestibular schwannoma,” “acoustic neuroma,” “stereotactic,” “radiation therapy,” “gamma knife,” and “surgery.” The search process is summarized in Figure 1. English, randomized clinical trials, prospective cohorts, and retrospective studies were selected. The titles and abstracts of these studies were screened, and pertinent full-text articles were reviewed for inclusion. The references of the identified studies were further queried for relevant studies.

Article Selection

Only studies that investigated NF2-VS with sufficient clinical information were included. Studies that reported on patients with spinal lesions, aggregated sporadic VS, or used other forms
of radiation other than single fraction SRS were excluded. Single patient case reports were also excluded. For studies with substantial overlapping patient populations, only the most recent publication was included. SRS studies utilizing either Gamma Knife Surgery and linear accelerator (LINAC) were included.

Data Extraction

Data on patient demographics, treatment parameters, treatment outcomes, complications and follow-up length were extracted. Outcome measures included local control, hearing preservation, trigeminal nerve preservation, facial nerve preservation, and recurrence. Reported outcomes and complication rates were obtained from the last clinical follow-up, unless otherwise noted. Hearing preservation was defined as the proportion of individuals who presented with serviceable hearing and maintained serviceable hearing at last follow-up. Serviceable hearing was defined as either a Gardner-Robertson (GR) grade I-II or an American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) class A-B. Facial nerve preservation was defined as the proportion of individuals who maintained a House-Brackmann (HB) grade I-II at last follow-up. All reported values represent aggregated data from each respective study.

Statistical Analysis

Statistical analyses were completed using R (v3.4.0; R Core Team, Vienna, Austria). Outcome measures between the SRS and surgery cohorts were compared using chi-square two-sample tests for equality of proportions on pooled patient data. Statistical significance was set at a \( P \) value < 0.05 for all analyses. Demographic and clinical measures are reported as aggregate weighted averages with equal waiting for each patient in SRS and surgery cohorts. Ranges and
standard deviations are also provided for the mean metrics reported across each reviewed SRS and surgical study.

Results

A total of 23 studies were identified between years 1992 and 2016, with 14 studies evaluating SRS (Table 1) and 9 studies evaluating surgery (Table 2) for NF2-VS [3, 10, 11, 26-44]. A total of 974 patients were included with 485 (49.8%) patients in the SRS and 489 (51.2%) patients in surgery cohorts. Demographic and clinical data were averaged across all patients in SRS and surgery cohorts to compare treatment modalities.

Radiosurgery and NF2-VS

Across studies, the mean age of the SRS cohort was 32.7 years (range: 15.2-40.0, SD: 7.0), the average marginal dose was 13.1 Gy (range: 12.0-18.0, SD: 1.5), and the average maximum dose was 27.5 Gy (range: 16.2-40, SD: 2.9). The mean tumor volume was 3.6 mL (range: 3.7-9.5, SD: 1.8), and mean follow-up was 5.2 years (range: 2.2-10.0, SD: 2.2). The mean 5-year local control rate was 74.5% (range: 62.0-92.0; SD: 12.1). The mean rates of hearing preservation, trigeminal nerve preservation, and facial nerve preservation were 40.1% (range: 0-78.0, SD: 23.9), 95.0% (range: 73.7-100, SD: 8.1), and 92.3% (range: 50.0-100, SD: 15.5), respectively. Seven SRS studies exceeded marginal doses of 14 Gy, while the remaining 7 SRS studies constrained marginal doses to 14 Gy. We separately tabulated these studies based on prescribed marginal dose to consider the possibility of differences in tumor control or functional outcomes due to
different dosing regimens. Pooled averages for SRS studies stratified by dosing regimen are provided in Table 1.

Surgery and NF2-VS

Across studies, the mean age of the surgery cohort was 26.3 years (range: 12.6-36.3, SD: 8.0). The mean tumor size was 2.4 cm (range: 1.0-3.1, SD: 1.1), and mean follow-up was 3.3 years (range: 1.1-8.0, SD: 2.4). The mean gross total resection rate was 86.6% (range: 33.3-100, SD: 22.1), and mean tumor recurrence rate, including patients who had either gross or subtotal resection, was 8.1% (range: 0-13.9, SD: 6.2). The mean hearing preservation rate was 52.0% (range: 13.6-65, SD: 21.2). The mean facial nerve preservation rate was 75.7% (range: 25.0-92.3, SD: 24.1). Across studies, mean preoperative tumor size (maximum diameter) was correlated with facial nerve preservation rate ($r = -.96$, $P = .04$), but was not correlated with hearing preservation rate ($r = -.51$, $P = .38$) or with the rate of local tumor control at last follow-up ($r = -.65$, $P = .35$).

Five of 9 reviewed series of surgical cases reported some type of complication rates. Among studies that reported postsurgical complication rates, there were no operative deaths among 268 cases. Perioperative mortality was 1.1%. CSF leak occurred in 3.1% of reported cases, and postoperative lower cranial nerve palsy resulted in 4.5% of reported cases. There were single reported instances of postoperative hospital readmission, meningitis, abducens palsy, postauricular seroma, and abdominal hematoma; however, such metrics were only reported in individual studies and could not be extrapolated in pooled analysis. No studies reported instances of wound infection or hematoma.
Outcomes of Radiosurgery versus Surgery for NF2-VS

The proportion of patients with hearing preservation was significantly lower for the pooled SRS cohort than the pooled surgery cohort at 29.4% (95% CI: 25.5-33.8) versus 38.0% (95% CI: 33.6-42.4), respectively (p = 0.006) (Figure 2). However, the pooled SRS cohort had significantly higher facial nerve preservation than the pooled surgery cohort at 90.9% (95% CI: 88.0-93.3) versus 75.7% (95% CI: 71.6-79.4), respectively (p < 0.001) (Figure 3). Across studies, average preoperative tumor volume was not correlated with rate of local tumor control at 5 years (r = .30, P = .57) or last follow-up (r = -.03, P = .94), or with hearing preservation rate (r = -.47, P = .17) or facial nerve preservation rate (r = .24, P = .50).

Discussion

The role of radiosurgery for the treatment of NF2-VS has yet to be clearly defined. In this systematic review, the authors evaluated the outcomes of NF2-VS patients following SRS and surgery. The results of our analysis suggest that SRS may be an effective treatment modality for NF2-VS.

Radiosurgery and NF2-VS

In recent decades, SRS has emerged as an effective treatment modality for sporadic VS, demonstrating high rates of tumor control and minimal side effects [24, 25, 45]. When taking into account patient comfort, quality of life, cost of treatment, and avoidance of potential surgical complications such as meningitis, hemorrhage, and CSF leak, SRS serves as an appealing
alternative to surgery [46]. However, the outcomes of SRS for NF2-VS require further elucidation. Despite advances in treatment, a majority of patients eventually develop significant bilateral hearing loss; thus, current management paradigms must balance a patient’s quality of life and need for intervention.

A primary objective of SRS is tumor control. Most of included studies reported good to excellent outcomes with an average 5-year local control rate of 74.5%, which is within the range previously described in the literature [35]. However, a number of studies reported local control rates at various follow-up periods, limiting direct comparisons. Nevertheless, when compared to the 90-98% tumor control rates for sporadic VS, the reported rates for NF2-VS were lower [47-50]. The reason for this discrepancy is unknown. Postulated explanations include differences in genetic background, multilobulated physiology, and younger age affecting the radiobiology of NF2-VS [10]. Specifically, older patients appear to have higher local control rates [10, 32]. In longitudinal studies of NF2, younger patients tend to have faster growth rates, possibly due to more aggressive phenotypes in younger individuals [51, 52]. Choi et al. evaluated the outcomes of 13 pediatrics NF2 patients treated with SRS and found a 3-year local control of only 35%, suggesting that adults and pediatrics NF2 patients exhibit different response to SRS [26]. Tumor volume may also be correlated with local control rates. Some studies have found that smaller tumor volumes at the time of treatment were the most significant predictor of outcomes, while another reported no correlation between outcomes and tumor size [10, 32, 33].

The preservation of cranial nerve functions is another critical challenge in the management of NF2-VS. Our review found that the rate of serviceable hearing preservation following SRS was
40%, ranging from 0% to 78% across studies. The wide range of reported values likely reflects heterogeneous baseline patient characteristics, radiation dosing, and variable follow-up lengths. The issue of administered dose merits special consideration, as current practices for SRS have evolved markedly over several decades of refinement [12, 29, 53]. In particular, it is generally well accepted in modern practice that a marginal dose of 14 Gy should not be exceeded to mitigate complications such as hearing loss or other cranial nerve morbidity. Some of our studies, in particular that of Linskey et al. [29], reflect practices from an earlier era involving higher dosing that could have biased our pooled analysis to reflect poorer hearing and cranial nerve outcomes than actually observed in current practice. To assess this possibility, we stratified the reviewed SRS studies based on whether the prescribed doses exceeded 14 Gy in any patient. We indeed observed modest trends towards favorable cranial nerve outcomes with studies restricting doses below 14 Gy (e.g., 42.5% vs. 38.9% hearing and 95.8% vs. 89.6% facial nerve preservation rates). Differences in outcomes between studies involving higher or lower dosing regimens were small, and, in our view, unlikely to have substantially affected our conclusions.

However, we note that our subgroup analysis was limited by considerable cross-patient variability in dosing within each individual study. Lower marginal doses may indeed reduce the rate of cranial nerve complications [54]. Multiple studies have reported lower rates of trigeminal and facial neuropathy at doses ≤ 14 Gy when compared to doses > 14 Gy in patients with NF2-VS [32, 55, 56]. Even including studies exceeding this guidelines, the rates of trigeminal and facial nerve preservation were very favorable across all SRS studies reviewed, at 95.0% and 92.3% respectively. These high rates are unsurprising as SRS leaves the trigeminal and facial nerves anatomically intact, making subsequent recovery more likely. Furthermore, continued
advances in tumor targeting are likely to further reduce hearing, trigeminal, and facial nerve morbidity in the future.

Tumor size has also been reported to predict hearing outcomes [57]. Patients with smaller tumors likely represent individuals either treated earlier in their disease course or have less aggressive phenotypes. Furthermore, earlier intervention has been found to be beneficial across a variety of treatment modalities for VS [10, 38, 58-60]. Hearing outcomes also depend on the marginal dose delivered, as studies in sporadic VS consistently demonstrate better hearing preservation with lower doses (e.g., 12-13 Gy). Mathieu et al. found that a marginal dose of $\leq 14$ Gy was significantly associated with better hearing preservation [32]. Conversely, Linskey et al. reported a 0% hearing preservation rate in patients treated with a median marginal dose of 18 Gy [29]. Thus, it is reasonable to conclude that the lowest effective marginal dose should be used in NF2 patients to maximize both hearing preservation and tumor control.

**Malignant Induction in NF2-VS**

Despite high efficacy and low complication rates, SRS has not been universally adopted for the management of NF2-VS. One concern has been potential secondary malignant induction in these patients [61]. As the mutation in NF2 affects a tumor suppressor gene, a concern of radiation is inducing a second “hit” in the “two-hit hypothesis” of tumorigenesis. Despite these concerns, evidence for malignant transformation of VS after SRS is limited due to the small number of observed cases [62, 63]. One recent literature review identified 59 cases of malignant VS cases [62]. Twenty-nine of 59 cases occurred after radiotherapy, 25 cases were spontaneous, and 5 cases occurred after microsurgery [62]. Among malignant cases occurring after radiosurgery, 41% occurred in patients suffering from NF2 [62]. However, a major limitation of published studies and case reports of SRS patients are reports of malignant transformation of VS without
histopathological confirmation of preexisting benign tumor. Among malignant cases reviewed by Seferis et al., only 9 of the 59 cases had histopathological confirmation of a benign lesion prior to SRS, making it uncertain to what extent radiotherapy contributed to malignant change [62]. Such associations are even more dubious in NF2 patients given their genetic predisposition. For this reason, NF2 patients have been excluded from meta-analyses assessing the attributable risk of SRS for malignant transformation of VS [63].

Our survey of the literature identified 9 studies describing 13 total NF2 patients with malignant induction following radiation-based treatments [33, 64-71]. A summary is provided in Table 3. In the largest of these studies, Baser et al. identified 1,348 NF2 patients at centers across North American and Europe and found that only 5 patients had malignant tumors following SRS [65]. Malignant peripheral nerve sheath tumors appear to be the most common malignant transformation, with most transformations occurring years after treatment. An important limitation of these studies is the lack of histopathological confirmation of a benign lesion prior to radiation therapy, which raises the possibility that the lesion may have already undergone malignant transformation prior to SRS. Among the 485 patients in the SRS cohort, only a single report of malignant induction was described by Rowe et al., in which a malignant glioma developed 3 years after SRS [33]. Moreover, when comparing the rates of reported malignant VS transformation in patients undergoing either surgery with or without adjuvant SRS, Maducdoc et al. identified four cases of malignant transformation in patients with sporadic VS who underwent surgical resection alone. These cases make malignant transformation in the absence of SRS even more plausible in NF2 patients due to their expected increased baseline risk. Thus, evidence remains inconclusive for an increased risk of malignant change in NF2 patients receiving SRS. Elucidation of this issue will require more studies with histopathological evidence of benign pretreatment lesions, as well as larger studies with longer follow-up. Ultimately, the limited and tenuous nature of existing evidence on malignant
transformation does not offset decades of progress validating radiotherapy as a safe and effective
treatment modality for VS [32, 55].

Surgery and NF2-VS

Microsurgical resection has long been the gold standard treatment for NF2-VS. Although SRS
appears to confer good tumor control and few side effects, current recommendations often limit
its application to patients with intracanalicular or small-to-medium-sized tumors [72].
Conversely, large (>3 cm in extracanalicular diameter), rapidly growing (≥2.5 mm/year) tumors
and patients with progressive neurological deficits (e.g., brainstem compression) are likely to
have poorer outcomes after primary SRS and may instead require surgical intervention [73].
Gross total resection was frequently achieved in the studies reviewed; consequently, recurrence
rates were relatively low. Moffat et al. reported a 13.9% overall recurrence rate, but the authors
found that tumor recurrence was not observed in any patient who had gross total resection [39].
Thus, these findings suggest that deliberate subtotal resection should only be reserved for select
cases (e.g., severe adherence to vital structures) or for hearing preservation in the only hearing
ear [38, 39, 42].

Serviceable hearing preservation was achieved in 46.9% of patients, ranging from 13.6% to 65%
across studies. Although NF2-VS tend to be more infiltrative on histology, these rates of hearing
preservation compare favorably to those of sporadic VS [74]. One potential explanation for the
similar rates is the timing of surgery. Early intervention in NF2-VS, when the tumor is still
small, may mimic the physiology of sporadic VS [38]. Facial nerve function after surgery also
remains critical for quality of life, and an overall preservation rate of 81.5% was found. Although
some prior studies did not find significant correlations between facial nerve outcomes and tumor
size, our analyses found increased rates of facial nerve preservation with smaller tumor sizes [11, 44]. Specifically, better facial nerve outcomes were predicted by smaller tumor diameters and older patient ages. Similar findings were confirmed by Moffat et al., who stratified tumors by their maximum diameters and found that tumors < 1.5 cm had 100% HB grade I-III, 1.5-2.4 cm tumors had 92% HB grade I-III, and 2.5-3.4 cm tumors had 85% HB grade I-III post-operatively [39].

It is also important to note that while operative morbidity and mortality have improved tremendously for surgical resection of VS, the risk of postsurgical complications remains and must be taken into account in deciding the optimal course of management in cases of NF2-VS. Of studies reporting data on postsurgical complications, we noted that although there were no reports of operative mortality, 30-day postoperative mortality was 1.1% and represents a considerable risk. Other risks reported in reviewed series of surgical cases include CSF leak (3.1% of cases), lower cranial nerve palsy (4.5% of reported cases) and meningitis (0.2% of cases), with zero cases of stroke reported. Such postsurgical complication risks were small but should be weighed against anticipated risks of SRS, particularly in older patients or patients with higher burdens of comorbidities that place them at higher risk of surgical complications.

**Radiosurgery versus Surgery for NF2-VS**

Direct comparisons between SRS and surgery outcomes for NF2-VS have been limited in the literature due to a paucity of cases and differences in treatment parameters, baseline characteristics, and follow-up lengths. In our analysis, hearing preservation rates were significantly higher in the surgery cohort, while facial nerve preservation rates were significantly
higher in the SRS cohort. We believe these findings partially reflect the changing management of NF2-VS in recent decades. SRS originally saw elevated rates of cranial neuropathies due to the use of high marginal doses, but advances in treatment planning within the last decade have resulted in dramatic improvements to cranial nerve morbidities. In a number of SRS studies reviewed, the authors specifically describe drastically lower facial nerve morbidities in a more recent subset of their patients [30, 32, 37, 56]. Similar improvements to hearing outcomes may also be possible with optimization of other parameters, such as cochlear dose [75-80]. Advances in surgical technique and intraoperative nerve monitoring in prior decades have similarly enabled improved rates of hearing preservation following surgery as well. Brackmann et al. described an institutional experience where modifications of the middle fossa craniotomy resulted in hearing preservation improving from 25.0% to 42.5% [38]. Furthermore, SRS patients in the reviewed studies tended to be older and a proportion had received prior surgical intervention. Thus, the overall rate of hearing and facial nerve preservation may actually be understated for SRS. By offering high rates of local control with improved facial nerve preservation, SRS may be the treatment of choice for patients with little to no functioning hearing at baseline. SRS and surgery are used in different clinical situations and may also play a complementary role in the management of NF2-VS. In the context of hearing rehabilitation strategies, surgery enables implantation of an auditory brain device at time of surgical resection, while SRS spares the cochlear nerve, allowing for the possibility of a cochlear impact. As treatment techniques evolve to reflect best practices, the outcomes of SRS and surgery will change. Thus, continued investigations will be required to determine whether the differences identified in this review reflect a true distinction or a selection bias.
Limitations

Several limitations were made apparent during data synthesis. First and foremost, there were likely systematic differences in pretreatment tumor size between the reviewed surgical and SRS cases of NF2-VS. For sporadic VS, it is generally well recognized in the literature that given similar tumor sizes, SRS provides superior hearing preservation than surgical resection. Across our reviewed studies of surgical resections, the mean tumor diameter was 2.4 cm. Many of the reviewed studies exclusively reported cases operated via a middle fossa approach, which is limited to smaller tumors likely associated with lower overall morbidity. On the other hand, tumors larger than 3-3.5 cm are generally too large to be treated with primary SRS [81], and the surgery cohort likely included a subset of large or giant VS cases not present in the SRS cohort. Unfortunately, very few studies reported the full distribution or even the range of tumor sizes across patients [41, 82]. Differences in tumor size almost certainly influenced rates of tumor control and functional outcomes such as cranial nerve preservation. Indeed, we observed a significant correlation between mean tumor diameter and rates of facial nerve preservation across surgical series, and such effects would likely have been more apparent were individual patient outcomes available. Another major limitation of this review was that surgical series reported maximal tumor diameters whereas SRS studies reported tumor volumes, making an accurate comparison of tumor size between treatment modalities impossible. A crude approximation using the assumption of a spherical lesion would yield an estimated average tumor volume of around 7.2 mL for the surgical patients, larger than the average reported tumor volume of 3.6 mL in patients receiving primary SRS. This observation, though tenuous, is in line with the fact that primary SRS is limited to treating small to moderate size tumors [81].
A second major limitation of our study was the shorter follow-up times reported when assessing tumor recurrence rates and functional outcomes in NF2-VS patients undergoing surgical resection (3.6 years) compared to primary SRS (6.1 years). Even the longer average follow-up time among patients in SRS studies (5.2 years) were inadequate to truly capture all possible incidences of tumor recurrence. Follow-up times for SRS were also inadequate to accurately assess hearing preservation, as it is known that hearing continues to deteriorate even beyond 5 years after SRS. With regard to surgical studies, it is known that the risk of tumor recurrence increases over time after surgical resection well beyond follow-up durations of 5 years. The fact that the surgical series reported follow-up lengths nearly twice as short as the SRS studies suggests that tumor recurrence rates are likely underestimated in our pooled surgical cohort relative to patients receiving SRS. Clinical follow-up durations of reviewed studies were even more limited for cranial nerve functions, specifically facial nerve preservation. Studies did not specifically report the follow-up lengths at which facial nerve function was last assessed, yet some studies reported ranges of follow-up periods indicating last clinical assessment of facial nerve function of less than one postoperative year. Such follow-up times are inadequate to accurately gauge long-term facial nerve function. Overall, there is a need for further studies incorporating longer follow-up not just for assessing tumor control but also involving comprehensive assessment of functional outcomes including hearing and cranial nerve preservation.

Several other factors also limited the strength of our conclusions. A number of studies aggregated both sporadic and NF2-VS patients and were therefore excluded from final data analysis. Variable reporting of outcome measures and differences in follow-up lengths between studies further limited comparisons. This reduced our sample size and overall ability to draw conclusions for a number of outcome measures.
Additionally, retrospective analyses are commonly constrained by the heterogeneity and selection bias of included studies. Differences in individual patient characteristics between the SRS and surgery cohorts may affect treatment outcomes, and may not have been accounted for in our analyses. Furthermore, quality of life is a crucial aspect to consider when evaluating alternative treatment modalities. Post-treatment complications, hearing and facial nerve preservation, and other neurological morbidity were reported and quantified in our analysis whenever possible, but very few studies attempted to directly report patient quality of life outcomes. There is need for further research on patients’ self-reported quality of life after surgery or SRS for treatment of NF2-VS.

Conclusions

SRS appears to be a safe and effective alternative to surgery for NF2-VS. Although rates of hearing preservation were higher in the surgery cohort, SRS demonstrated high rates of local control as well as higher rates of facial nerve preservation. With the recent advances in treatment planning and dose delivery, outcomes for SRS will continue to improve and likely serve as an invaluable, minimally invasive, alternative treatment to surgery particularly for patients with poor baseline hearing. Understanding the advantages and limitations of SRS compared to microsurgery will enable physicians and patients to make better informed decisions regarding their care.
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References


Chung


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Figure Legends

Figure 1. Article selection

Figure 2. Test of proportions for serviceable hearing preservation with 95% confidence intervals

Figure 3. Test of proportions for facial nerve preservation with 95% confidence intervals
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<td>13.9 (10-20)</td>
<td>NR</td>
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<td>NR</td>
<td>92.3</td>
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<td>70.0</td>
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<td>13.0 (10-15)</td>
<td>26.8 (23-31)</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
<td>90.0</td>
</tr>
<tr>
<td>Sharma et al., 2010</td>
<td>30</td>
<td>54</td>
<td>29.0</td>
<td>2.2*</td>
<td>33.0</td>
<td>3.7</td>
<td>12.0* (10-15)</td>
<td>NR</td>
<td>67.3</td>
<td>66.7</td>
<td>100</td>
<td>96.9</td>
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<td>103</td>
<td>12</td>
<td>34.9</td>
<td>5.9*</td>
<td>24.0</td>
<td>1.5*</td>
<td>12.0* (5-20)</td>
<td>NR</td>
<td>74.5</td>
<td>40.0</td>
<td>96.9</td>
<td>97.7</td>
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<td>34</td>
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<td>3.3</td>
<td>13.2 (5-20)</td>
<td>28.3 (21.8-40)</td>
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<td>93.9</td>
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<td>Kim et al., 2016</td>
<td>7</td>
<td>8</td>
<td>NR</td>
<td>8.4</td>
<td>23.5</td>
<td>5.6</td>
<td>13.0* (10-14)</td>
<td>NR</td>
<td>50.0</td>
<td>40.0</td>
<td>NR</td>
<td>NR</td>
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<tr>
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<td>4</td>
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<td>28.5</td>
<td>10.0</td>
<td>0</td>
<td>9.5</td>
<td>13.0 (12-14)</td>
<td>NR</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>100</td>
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<td>NR</td>
<td>4.4*</td>
<td>11.1</td>
<td>2.0*</td>
<td>12.0* (11-12)</td>
<td>NR</td>
<td>80.2</td>
<td>78.0</td>
<td>NR</td>
<td>100</td>
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<tr>
<td>Choi et al., 2014</td>
<td>13</td>
<td>18</td>
<td>15.2</td>
<td>3.0</td>
<td>NR</td>
<td>4.8</td>
<td>12.4 (NR)</td>
<td>NR</td>
<td>35.3</td>
<td>52.0</td>
<td>NR</td>
<td>100</td>
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<tr>
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<td>30</td>
<td>36</td>
<td>32.5</td>
<td>4.0*</td>
<td>2.3</td>
<td>3.2*</td>
<td>12.1 (8-14)</td>
<td>24.4</td>
<td>66.0</td>
<td>37.3</td>
<td>97.2</td>
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<tr>
<td>Rowe et al., 2008</td>
<td>96</td>
<td>12</td>
<td>28.9</td>
<td>NR</td>
<td>20.5</td>
<td>NR</td>
<td>13.4 (NR)</td>
<td>NR</td>
<td>62.0</td>
<td>(5 yr)</td>
<td>98.0</td>
<td>95.0</td>
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<td>Sun et al., 2014</td>
<td>46</td>
<td>73</td>
<td>35.0</td>
<td>9.1*</td>
<td>25.3</td>
<td>5.1</td>
<td>12.9 (10-14)</td>
<td>27.5</td>
<td>87.0</td>
<td>33.3</td>
<td>92.0</td>
<td>95.0</td>
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<tr>
<td><strong>Pooled</strong></td>
<td>214</td>
<td>28</td>
<td>30.0</td>
<td>6.4</td>
<td>17.4</td>
<td>4.3</td>
<td>12.9 (8-14)</td>
<td>26.2 (16.2-40)</td>
<td>68.2</td>
<td>42.5</td>
<td>96.3</td>
<td>95.8</td>
</tr>
<tr>
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<td>485</td>
<td>63</td>
<td>32.7</td>
<td>5.2</td>
<td>23.0</td>
<td>3.6</td>
<td>13.1 (5-20)</td>
<td>27.5</td>
<td>75.1</td>
<td>40.1</td>
<td>95.0</td>
<td>92.3</td>
</tr>
<tr>
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</tr>
<tr>
<td></td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(16.2-40)</td>
<td></td>
<td></td>
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</tbody>
</table>

VS = vestibular schwannoma, NR = not reported, * = median
Table 2. Summary of surgery studies for NF2-associated VS

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Surgical Approach</th>
<th>Patient, n</th>
<th>VS, n</th>
<th>Mean Age, yr</th>
<th>Mean Follow-up, yr</th>
<th>Mean Tumor Diameter, cm</th>
<th>Gross Total Resection, %</th>
<th>Tumor Recurrence, %</th>
<th>Hearing Preservation, %</th>
<th>Facial Nerve Preservation, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brackmann et al., 2001</td>
<td>MF</td>
<td>28</td>
<td>40</td>
<td>22.6</td>
<td>1.1</td>
<td>1.1</td>
<td>100</td>
<td>0.3</td>
<td>64.8⁎</td>
<td>92.3</td>
</tr>
<tr>
<td>Choi et al., 2014</td>
<td>NR</td>
<td>4</td>
<td>6</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>33.3</td>
<td>NR</td>
<td>NR</td>
<td>25.0</td>
</tr>
<tr>
<td>Friedman et al., 2011</td>
<td>MF</td>
<td>37</td>
<td>55</td>
<td>21.6</td>
<td>2.1</td>
<td>1.0</td>
<td>96.3</td>
<td>NR</td>
<td>NR</td>
<td>90.9</td>
</tr>
<tr>
<td>Moffat et al., 2013</td>
<td>TL</td>
<td>128</td>
<td>148</td>
<td>29.5</td>
<td>2.0</td>
<td>3.1</td>
<td>90.0</td>
<td>NR</td>
<td>NR</td>
<td>61.3</td>
</tr>
<tr>
<td>Nowak et al., 2015</td>
<td>RS, RL, MF</td>
<td>30</td>
<td>51</td>
<td>25.7</td>
<td>3.3</td>
<td>2.8</td>
<td>100</td>
<td>9.8</td>
<td>57.0</td>
<td>49.0</td>
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<tr>
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<td>MF</td>
<td>38</td>
<td>48</td>
<td>36.3</td>
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<td>3.1</td>
<td>92.0</td>
<td>2.6</td>
<td>57.0</td>
<td>52.1</td>
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<tr>
<td>Samii et al., 2008</td>
<td>MF</td>
<td>145</td>
<td>198</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>85.0</td>
<td>NR</td>
<td>NR</td>
<td>65.0</td>
</tr>
<tr>
<td>Slattery et al., 2007</td>
<td>MF</td>
<td>35</td>
<td>47</td>
<td>12.6</td>
<td>2.8</td>
<td>1.1</td>
<td>92.0</td>
<td>NR</td>
<td>NR</td>
<td>57.5</td>
</tr>
<tr>
<td>Tysome et al., 2012</td>
<td>TL</td>
<td>44</td>
<td>50</td>
<td>8.0</td>
<td>NR</td>
<td>NR</td>
<td>78.0</td>
<td>0</td>
<td>20.0⁰</td>
<td>89.0</td>
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<tr>
<td>Pooled</td>
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<td>489</td>
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<td>2.4</td>
<td>86.6</td>
<td>8.1</td>
<td>52.0</td>
<td>75.7</td>
</tr>
</tbody>
</table>

VS = vestibular schwannoma, MF = middle fossa, TL = translabyrinthine, RS = retrosigmoid, NR = not reported, ⁎ = evaluated < 12 months, ⁎⁎ = evaluated ≥ 12 months, ⁎⁎⁎ = not specified
### Table 3. Summary of studies reporting malignant induction after radiation-based treatment

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Age, yr</th>
<th>Sex</th>
<th>Marginal Dose, Gy</th>
<th>Radiation Technique</th>
<th>Interval after Treatment, yr</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bari et al., 2002</td>
<td>28</td>
<td>F</td>
<td>15.0</td>
<td>SRS</td>
<td>3.5</td>
<td>Malignant peripheral nerve sheath tumor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Malignant peripheral nerve sheath tumor</td>
</tr>
<tr>
<td>Baser et al., 2000</td>
<td>32*</td>
<td></td>
<td>NR</td>
<td>SRS</td>
<td>NR</td>
<td>Malignant peripheral nerve sheath tumor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NR</td>
<td>SRS</td>
<td>NR</td>
<td>Malignant peripheral nerve sheath tumor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NR</td>
<td>SRS</td>
<td>NR</td>
<td>Malignant meningioma</td>
</tr>
<tr>
<td>Carlson et al., 2010</td>
<td>25</td>
<td>F</td>
<td>54.0</td>
<td>fSRT</td>
<td>0.8</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>Ho et al., 2002</td>
<td>14</td>
<td>F</td>
<td>22.0</td>
<td>fSRT</td>
<td>0.6</td>
<td>Rapid growth of bilateral VS (&gt; 2x size increase)</td>
</tr>
<tr>
<td>Husseini et al., 2011</td>
<td>20</td>
<td>M</td>
<td>13.5</td>
<td>SRS</td>
<td>5.0</td>
<td>Malignant peripheral nerve sheath tumor</td>
</tr>
<tr>
<td>McEvoy et al., 2003</td>
<td>22</td>
<td>M</td>
<td>15.0</td>
<td>SRS</td>
<td>2.0</td>
<td>Rapid growth of ipsilateral VS (&gt; 3x size increase)</td>
</tr>
<tr>
<td>Noren et al., 1988</td>
<td>18</td>
<td>F</td>
<td>20.0</td>
<td>SRS</td>
<td>6.0</td>
<td>Triton</td>
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<tr>
<td>Rowe et al., 2008</td>
<td>NR</td>
<td>F</td>
<td>13.4*</td>
<td>SRS</td>
<td>3.0</td>
<td>Malignant glioma</td>
</tr>
<tr>
<td>Thomsen et al., 2000</td>
<td>19</td>
<td>F</td>
<td>12.0</td>
<td>SRS</td>
<td>0.6</td>
<td>Glioblastoma</td>
</tr>
</tbody>
</table>

* = Mean of cohort, NR = not reported, F = female, M = male, VS = vestibular schwannoma
PubMed (n = 581) → Scopus (n = 40) → Web of Science (n = 333) → Records after duplicates removed (n = 494) → Title and Abstract Review (n = 494) → Full-text articles assessed for eligibility (n = 88) → Studies included in qualitative synthesis (n = 23)

Records excluded (n = 406)
- Case reports
- Non-English
- Irrelevant

Records excluded (n = 65)
- Full-text unavailable
- Insufficient data
- Duplicate
- Irrelevant
[Diagram content not transcribed as it is a data visualization and cannot be accurately represented in text form.]
**Abbreviations and Acronyms**

NF2: Neurofibromatosis Type II

VS: Vestibular schwannoma

NF2-VS: Neurofibromatosis Type II associated vestibular schwannomas

SRS: Stereotactic radiosurgery

GR: Gardner-Robertson

AAO-HNS: American Academy of Otalaryngology-Head and Neck Surgery

HB: House-Brackmann