Systematic review and meta-analysis of the technique of subtotal resection and stereotactic radiosurgery for large vestibular schwannomas: a “nerve-centered” approach

Daniele Starnoni, MD,1 Roy Thomas Daniel, MCh,1 Constantin Tuleasca, MD,1,3 Mercy George, MS,2 Marc Levivier, MD, PhD,1 and Mahmoud Messerer, MD1

1Neurosurgery Service and Gamma Knife Center and 2ENT Service, Centre Hospitalier Universitaire Vaudois (CHUV), Faculty of Biology and Medicine, University of Lausanne; and 3Swiss Federal Institute of Technology (EPFL), Laboratory of Transmission Signal (LTS5), Lausanne, Switzerland

OBJECTIVE During the last decade, the primary objective for large vestibular schwannoma (VS) management has progressively shifted, from tumor excision to nerve preservation by using a combined microsurgical and radiosurgical approach. The aim of this study was to provide a systematic review and meta-analysis of the available literature regarding the combined strategy of subtotal resection (STR) followed by stereotactic radiosurgery (SRS) for large VSs.

METHODS The authors performed a systematic review and meta-analysis in compliance with the PRISMA guidelines for article identification and inclusion using the PubMed, Embase, and Cochrane databases. Established inclusion criteria were used to screen all identified relevant articles published before September 2017 without backward date limit.

RESULTS The authors included 9 studies (248 patients). With a weighted mean follow-up of 46 months (range 28–68.8 months), the pooled rate of overall tumor control was 93.9% (95% CI 91.0%–96.8%). Salvage treatment (second STR and/or SRS) was necessary in only 13 (5.24%) of 18 patients who experienced initial treatment failure. According to the House-Brackmann (HB) grading scale, functional facial nerve preservation (HB grade I–II) was achieved in 96.1% of patients (95% CI 93.7%–98.5%). Serviceable hearing after the combined approach was preserved in 59.9% (95% CI 36.5%–83.2%).

CONCLUSIONS A combined approach of STR followed by SRS was shown to have excellent clinical and functional outcomes while still achieving a tumor control rate comparable to that obtained with a total resection. Longer-term follow-up and larger patient cohorts are necessary to fully evaluate the rate of tumor control achieved with this approach.


KEY WORDS combined approach; vestibular schwannoma; surgery; radiosurgery; Gamma Knife

The treatment of large vestibular schwannomas (VSs) has traditionally focused primarily on achieving total excision of the tumor. This strategy has been associated with a significant rate of facial and cochlear nerve deficits directly related to the surgery.1,21,45

Over the last decade, there has been a progressive shift of focus from tumor excision to nerve preservation as the primary objective, and this has been achieved by the use of a combination of subtotal resection (STR) and subsequent stereotactic radiosurgery (SRS).4

The goal of this strategy is to perform an intracapsular debulking focusing on reducing tumor size to render the tumor volume compatible for treatment with SRS.

With increasing interest generated in this strategy at several centers worldwide, this article attempts to analyze the existing literature through a systematic review of this novel trend in the treatment of large VSs. Experience with this treatment paradigm is limited, and therefore functional and surgical outcomes should be updated through a meta-analysis approach of published data.

Methods

Search Strategy and Selection Criteria

Following PRISMA guidelines and recommendations,29 we conducted a systematic search using the PubMed, Embase, and Cochrane databases. All studies published before September 2017 were screened. There was no backward date limit.

The following medical subject headings (MeSH) and ABBREVIATIONS

GKRS = Gamma Knife radiosurgery; GR = Gardner-Robertson; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; HB = House-Brackmann; SRS = stereotactic radiosurgery; STR = subtotal resection; VS = vestibular schwannoma.


INCLUDE WHEN CITING DOI: 10.3171/2017.12.FOCUS17669.
free text terms were used: “radiosurgery” OR “stereotactic radiosurgery” OR “gamma knife” OR “linear accelerator” AND “surgery” OR “resection” AND “acoustic neuroma” OR “vestibular schwannoma.”

No language restrictions were applied. The “related articles” function was used to obtain any relevant reports. We manually reviewed the reference lists of identified studies for further inclusions. When duplicate studies were published with accumulating numbers of patients or increased duration of follow-up, only the one reporting the entire necessary outcomes was included.

Eligibility was independently assessed by 2 authors (D.S. and M.M.), and differences were resolved with the help of a third author (R.T.D.) and consensus.

Study Selection
Studies were eligible if they met the following criteria: 1) included patients with large VSs (defined as Koos grade IV and/or size more than 3 cm in diameter) who were not considered eligible for up-front SRS; 2) microsurgical resection represented the first-line treatment; and 3) surgery was followed by SRS as treatment for the residual tumor, in the frame of a planned combined approach, with surgery and SRS.

Studies that encompassed the use of SRS for progressive tumor growth or recurrence without a subgroup analysis were excluded. We also excluded studies in which the reported outcome data after an STR were not distinguishable from cases undergoing a total or near-total resection.

Data Abstraction
The title and abstract of each study were screened initially for relevance by one investigator (D.S.) under the supervision of the second investigator (M.M.), and then full-text manuscripts were reviewed against specific inclusion criteria. Two authors (D.S. and M.M.) independently abstracted data on the patient and tumor characteristics, clinical data, and radiological and clinical outcomes after combined approach.

When a combined approach (STR followed by SRS) was applied to a subgroup of patients, only this subgroup was considered for data extraction and analysis.

Facial nerve function was classified according to the House-Brackmann (HB) grading scale,18 as uniformly reported in the screened reports. We further considered the HB grades as representing “functional” (grade I or II) and “not functional” (grade ≥ III) status. Hearing was graded according to the Gardner-Robertson (GR) classification scale12 and defined as “serviceable” (grade I or II) and “not serviceable” (grade ≥ III). In cases in which the hearing function was assessed by other classification systems, we considered as serviceable hearing a pure tone audiogram < 50 dB and/or the speech discrimination score > 50%.12

Tumor characteristics, when specified, were collected and reported as preoperative and pre-SRS mean tumor diameter (the largest diameter after measuring the 3 axes) and mean tumor volume.

Tumor control after the combined approach was defined as “stable” or “decreased” in size.

Quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group system.3 Disagreements were resolved by consensus.

Statistical Analysis
Weighted summary rates were determined using meta-analysis models. Testing for heterogeneity was performed for each meta-analysis. In cases of heterogeneity, a binary random-effects model (DerSimonian-Laird method) was used in some of the analysis assuming that the included studies were a random sample from a hypothetical population; otherwise, a binary fixed-effects model with inverse variance weighting was employed.

The OpenMeta(Analyst) from the Agency for Healthcare Research and Quality was used to perform these analyses.

Pooled estimates using meta-analytical techniques were obtained for the outcome and facial and cochlear nerve function after a combined approach, which followed binomial distributions.

Results

Literature Search
The search strategy identified a total of 962 studies (Fig. 1). Twenty-nine publications were retrieved for full-text analysis on the basis of the title and abstract.

After careful evaluation, 20 studies were excluded from our review. Finally, a total of 9 studies including 248 patients were included in this review.

Cohort Description and Treatment Strategy
Table 1 shows the retrieved studies, population characteristics, and treatment strategy. The 9 retrieved studies reported on outcome of patients harboring large VSs and treated with a combined approach of STR followed by adjuvant SRS. In 6 studies, a subtotal intracapsular decompression was part of a planned combined therapeutic strategy,8,11,19,34,38,50 while in the other 3, an STR was the result of an intraoperative decision based on the tumor capsule adhering to the facial and cochlear nerves.20,35,53

In 3 studies neurofibromatosis was an exclusion criterion,8,35,53 while in the remaining series exclusion criteria were not specified, but since only 2 patients with neurofibromatosis were present,20 they were included in the analysis.

In 2 studies35,38 a combined approach was applied only to a subgroup of patients; therefore, only these patients were considered for analysis. In one of these 2 studies,35 patient characteristics such as sex and median age data were not reported separately and could not be retrieved.

A total of 248 patients were included in our study. Data on sex and median age were available only for 240 patients. There were 106 males (44.2%) and 134 females (55.8%) (Table 1).

Microsurgical Technique
The surgical approach was reported in only 6 studies,8,11,19,20,34,50 A retrosigmoid approach was the only surgical procedure in 4 studies,8,11,19,34 in Iwai et al.,20 a trans-
petrosal transtentorial approach was performed for one case in which the patient presented with nonserviceable hearing function. The same strategy was adopted by van de Langenberg et al., who performed a retrosigmoid approach in 50% of the cases and a translabyrinthine approach in the remaining cases.

**Radiosurgery and/or Hypofractionated Radiotherapy Technique**

Gamma Knife radiosurgery (GKRS) was performed in 240 patients (96.8%). Radwan et al. performed hypofractionated SRS in 8 patients (3.2%) who went on to make a recovery from a new cranial nerve deficit lasting more than 3 months and/or a residual tumor volume greater than 3 cm$^3$.

The mean interval between surgery and SRS was reported in all but a single study and ranged from 2.9 to 9.5 months (median 6.1 months). The tumor margin dose ranged from 11 to 14 Gy for GKRS.

**Tumor Control**

Table 2 shows the preoperative tumor size and that at the time of SRS (mean tumor diameter and mean tumor volume). The mean tumor diameter at SRS was reported in only 3 studies; however, the mean tumor volume was reported in all but one study and ranged from 1.16 to 9.35 cm$^3$.

Pooled overall tumor control rate (Fig. 2), after a weighted mean follow-up of 46 months (range 28–68.8 months), was 93.9% (95% CI 91.0%–96.8%) and achieved in 230 patients. A binary fixed-effects estimate analysis was used ($p = 0.681$, test for heterogeneity).

Treatment failure was shown in 18 patients (7.26%); second-stage surgery or SRS was performed in 9 of them, 4 patients underwent a new combined approach, and the remaining 5 were observed and remained stable over time.

**Functional Outcome**

Follow-up clinical data on facial nerve function were reported in all but one study, and a random-effects pooled analysis ($p < 0.001$, test for heterogeneity) showed a facial nerve preservation rate (HB grade I–II) of 96.1% (95% CI 93.7%–98.5%) after a combined microsurgical and SRS approach (Table 3 and Fig. 3). No new case of permanent functional deterioration was described after
### TABLE 1. Population characteristics and treatment strategy

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Period</th>
<th>GRADE Rating</th>
<th>No. of Pts</th>
<th>Mean Age in Yrs (range)</th>
<th>M/F Ratio</th>
<th>Combined Approach</th>
<th>Surgical Approach</th>
<th>Mean Interval from Op to SRS in Mos (range)</th>
<th>Mean Tumor Margin Dose in Gy (range)</th>
<th>Mean FU in Mos (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iwai et al., 2003</td>
<td>1994–2000</td>
<td>Very low</td>
<td>14</td>
<td>47 (18–64)</td>
<td>6:8</td>
<td>STR + GKRS</td>
<td>13 (92.86%) retrosigmoid; 1 (7.14%) transpetrosal transtentorial</td>
<td>2.9 (1–6)</td>
<td>12.1 (10–14.1)</td>
<td>32 (12–72)</td>
</tr>
<tr>
<td>Park et al., 2006</td>
<td>1990–1999</td>
<td>Very low</td>
<td>8</td>
<td>NR (range)</td>
<td>NR</td>
<td>STR + GKRS</td>
<td>NR</td>
<td>NR (1–6)</td>
<td>12 (6–12)</td>
<td>46 (12–73)</td>
</tr>
<tr>
<td>Yang et al., 2008</td>
<td>1998–2004</td>
<td>Very low</td>
<td>61</td>
<td>41 (18–67)</td>
<td>20:41</td>
<td>STR + GKRS</td>
<td>5.8 (0.3–95.7)</td>
<td>12.5 (9–14)</td>
<td>53.7 (24.1–102.2)</td>
<td></td>
</tr>
<tr>
<td>van de Langenberg et al., 2011</td>
<td>2002–2009</td>
<td>Very low</td>
<td>50</td>
<td>52 (21–84)</td>
<td>28:22</td>
<td>Planned STR + GKRS</td>
<td>25 (50%) retrosigmoid; 25 (50%) translabyrinthine</td>
<td>8.5 (2–24)</td>
<td>11 (9.4–11.9)</td>
<td>33.8 (12–84)</td>
</tr>
<tr>
<td>Pan et al., 2012</td>
<td>2003–2008</td>
<td>Low</td>
<td>18</td>
<td>50 (NR)</td>
<td>10:8</td>
<td>Planned STR + GKRS</td>
<td>Retrosigmoid</td>
<td>3.6 (NR)</td>
<td>12 (NR)</td>
<td>57.7 ± 3.3</td>
</tr>
<tr>
<td>Iwai et al., 2015</td>
<td>2000–2013</td>
<td>Low</td>
<td>40</td>
<td>60.5 (33–82)</td>
<td>19:21</td>
<td>Planned STR + GKRS</td>
<td>Retrosigmoid</td>
<td>3 (1–12)</td>
<td>12 (10–12)</td>
<td>65 (18–156)</td>
</tr>
<tr>
<td>Radwan et al., 2016</td>
<td>NR</td>
<td>Very low</td>
<td>17</td>
<td>55.8 (37–77)</td>
<td>5:12</td>
<td>9 (52.9%) planned STR + GKRS; 8 (47.0%) planned STR + HF SRS</td>
<td>NR</td>
<td>9.53 (2–50)</td>
<td>12.5 (12–14)</td>
<td>28 (8–116)</td>
</tr>
<tr>
<td>Daniel et al., 2017</td>
<td>2010–2016</td>
<td>Low</td>
<td>32</td>
<td>51.7 (32.5–85)</td>
<td>13:19</td>
<td>Planned STR + GKRS</td>
<td>Retrosigmoid</td>
<td>6.3 (3.8–13.9)</td>
<td>12 (11–12)</td>
<td>29 (4–78)</td>
</tr>
</tbody>
</table>

FU = follow-up; HF = hypofractionated; NR = not reported; pts = patients.

### TABLE 2. Tumor control after combined subtotal resection and stereotactic radiosurgery

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Pts</th>
<th>Mean Tumor Diameter (mm)</th>
<th>Mean Tumor Residual Vol in cm³ (range)</th>
<th>Residual Tumor Control After Combined Approach (%)</th>
<th>Mean FU in Mos (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Preop</td>
<td>At GKRS (range)</td>
<td>Preop</td>
<td>At GKRS (range)</td>
</tr>
<tr>
<td>Iwai et al., 2003</td>
<td>14</td>
<td>6 pts (43%) 30–40; 6 pts (43%) 40–50; 2 pts (14%) &gt;50</td>
<td>18.9 (9.8–36.1)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Park et al., 2006</td>
<td>8</td>
<td>36.4 (range 30–47.2)</td>
<td>NR</td>
<td>26.8 (13.5–55.1)</td>
<td>4.6 (NR)</td>
</tr>
<tr>
<td>Fuentes et al., 2008</td>
<td>8</td>
<td>39.38 (range 35–45)</td>
<td>18 (9–20)</td>
<td>NR</td>
<td>1.16 (0.31–2.20)</td>
</tr>
<tr>
<td>Yang et al., 2008</td>
<td>61</td>
<td>NR</td>
<td>NR</td>
<td>20.6 (4.1–44.5)</td>
<td>3.65 (0.52–15.50)</td>
</tr>
<tr>
<td>van de Langenberg et al., 2011</td>
<td>50</td>
<td>35 (range 26–54)</td>
<td>NR</td>
<td>14.9 (4.1–36.1)</td>
<td>3.34 (0.22–11.8)</td>
</tr>
<tr>
<td>Pan et al., 2012</td>
<td>18</td>
<td>NR</td>
<td>NR</td>
<td>17.5 ± 1.1</td>
<td>9.35 ± 1.02</td>
</tr>
<tr>
<td>Iwai et al., 2015</td>
<td>40</td>
<td>32.5 (range 25–52)</td>
<td>18.6 (9.1–27.1)</td>
<td>NR</td>
<td>3.3 (0.4–10.4)</td>
</tr>
<tr>
<td>Radwan et al., 2016</td>
<td>17</td>
<td>NR</td>
<td>NR</td>
<td>13.1</td>
<td>2.94 (0.42–9.96)</td>
</tr>
<tr>
<td>Daniel et al., 2017</td>
<td>32</td>
<td>33.2 (range 20–45)</td>
<td>NR</td>
<td>12.5 (1.47–34.9)</td>
<td>3.5 (0.5–12.8)</td>
</tr>
</tbody>
</table>

* Data bridging these 2 columns indicate that the tumor either decreased in size or remained the same size.
SRS, but rather a progressive facial nerve recovery after SRS was shown in 17 patients at the time of last follow-up compared with the early postoperative status.

Data on cochlear nerve function before and after the combined approach were reported and collected in 7 studies and classified according to the GR classification in all but one. In van de Langenberg et al., the classification of the American Academy of Otolaryngology–Head and Neck Surgery was used; classes A and B were considered as serviceable hearing and were assimilated into GR grade I–II.

Therefore, reported preoperative serviceable hearing (GR grade I–II) was present in 63 patients (27.16%) for whom preoperative hearing status was reported. The random-effects pooled rate of cochlear nerve preservation (p < 0.001, test for heterogeneity) was 73.4% (95% CI 56.9%–89.9%) at early postoperative follow-up, and this decreased to 59.9% (95% CI 36.5%–83.2%) following SRS, with a weighted mean follow-up of 46 months (range 28–68.8 months) (Fig. 3).

Quality of Evidence

Based on the GRADE assessment, the certainty of the evidence and the strength of the data were low in 3 studies and very low in the remaining 6 studies.

Discussion

The management of large VSs remains challenging and a matter of ongoing debate, especially with regard to facial and cochlear nerve function preservation.

Although SRS, for small- to medium-sized lesions (Koos grade I–III), represents a valuable alternative treatment with a high rate of tumor control and functional nerve preservation, it does not represent an eligible upfront treatment for large VSs (Koos grade IV and/or more than 3 cm) because of the need for surgical decompression that arises due to the risk of clinical deterioration during transient tumor expansion after SRS.

The high-quality outcomes achieved in patients with smaller lesions treated with SRS have considerably increased expectations in patients harboring larger VSs and led several centers to change their treatment paradigm. A combined approach including partial/subtotal removal of the lesion followed by SRS has been increasingly adopted as the main strategy for preserving cranial nerve function while achieving tumor growth control.

### TABLE 3. Facial and cochlear nerve preservation after combined subtotal resection and stereotactic radiosurgery

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Pts</th>
<th>No. of Pts w/ Serviceable Hearing (GR grade I or II)</th>
<th>No. of Pts w/ Functional Facial Nerve (HB grade I or II)</th>
<th>Mean FU in Mos (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Preop</td>
<td>Postop</td>
<td>Post-SRS (last FU)</td>
</tr>
<tr>
<td>Iwai et al., 2003</td>
<td>14</td>
<td>3 (21.43%)</td>
<td>1 (33.33%)</td>
<td>1 (33.33%)</td>
</tr>
<tr>
<td>Park et al., 2006</td>
<td>8</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Fuentes et al., 2008</td>
<td>8</td>
<td>1 (12.5%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Yang et al., 2008</td>
<td>61</td>
<td>10 (16.39%)</td>
<td>5 (50%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>van de Langenberg et al., 2011</td>
<td>50</td>
<td>4 (8%)</td>
<td>1 (25%)</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>Pan et al., 2012</td>
<td>18</td>
<td>11 (61.11%)</td>
<td>11 (100%)</td>
<td>11 (100%)</td>
</tr>
<tr>
<td>Iwai et al., 2015</td>
<td>40</td>
<td>14 (35%)</td>
<td>11 (78.57%)</td>
<td>6 (42.85%)</td>
</tr>
<tr>
<td>Radwan et al., 2016</td>
<td>17</td>
<td>8 (47.06%)</td>
<td>8 (100%)</td>
<td>7 (87.5%)</td>
</tr>
<tr>
<td>Daniel et al., 2017</td>
<td>32</td>
<td>13 (40.63%)</td>
<td>10 (76.92%)</td>
<td>10 (76.92%)</td>
</tr>
</tbody>
</table>

* Few patients with no functional facial nerve preoperatively recovered to a functional grade after treatment; therefore, the rate was calculated on the whole group.
FIG. 3. Graphic representation showing pooled rates of functional facial nerve and serviceable hearing preservation after STR and at long-term follow-up after SRS. FU = follow-up.
The mechanical stress associated with direct dissection can be reduced or avoided in cases of STR, and STR represents the “nerve-centered” tumor surgery approach inherent in the combined approach. Apart from the obvious benefit of excellent facial nerve preservation rates, this surgical philosophy also reintegrates the possibility of preserving auditory function as part of the treatment, a factor that is often ignored in the pursuit of a total excision in surgery for large VSs (i.e., the traditional treatment paradigm). Two strategies involving an excision that is less than total have been described for this combined-therapy paradigm. One strategy consists of a planned STR focusing on reducing the tumor size to render the tumor volume compatible with SRS. The other strategy involves an intraoperative decision on whether to perform a subtotal or near-total extirpation (leaving only a small tumor remnant) in cases in which tumor capsule dissection may impede the functional preservation.

Compared with this last approach, the planned combined approach seems to be associated with the best functional outcome, which can be explained by the fact that no dissection is attempted between the plane of the nerve and the tumor capsule, thereby maximizing the chances of a normally functioning nerve at the end of surgery.

**Facial Nerve Outcome**

Our systematic review was able to show an excellent outcome among all retrieved studies with a pooled rate of functional facial nerve preservation (HB grade I–II) of 96.1% on long-term follow-up.

Reported rates of good functional outcomes after gross-total resection vary according to the experience and competence of the specific center, with good facial nerve function in up to 75% cases in the hands of skillful surgeons. The association among the size of the tumor, degree of resection, and outcome has been assessed and shown to be a main predictor for facial nerve preservation.

A recent meta-analysis showed that good facial nerve outcome was achieved in 74.6% and 47.3% of patients undergoing near-total and gross-total resection, respectively, compared with a rate of 92.5% in patients receiving an STR.

In some series, a progressive facial nerve recovery to a serviceable state after SRS has been shown, and in none of the retained articles in our review was a deleterious effect of SRS reported. The reported outcome of large series of centers of high experience and expertise for SRS, facial nerve functional degradation after GKRS, has become anecdotal due to the introduction of robotization. Notably, a progressive rate of facial nerve recovery at long-term follow-up following SRS has been shown, compared with the postoperative period, emphasizing the importance of a long-term evaluation to assess the outcome after adequate tumor shrinkage following SRS.

**Hearing Preservation**

The pooled rate of cochlear nerve preservation after surgery was 73.4% and deteriorated to a rate of 59.9% at last examination following SRS; the rate ranged between 25% in the series of van de Langenberg et al. who reported hearing preservation in only 1 of 4 patients with serviceable presurgical hearing, and 100% in the study by Pan et al.

The disparity among the results reported in the various series may be largely related to the different rates of presurgical serviceable hearing, which do not necessarily correlate with the size of VS, but may also be due to the specific philosophical approach of each surgeon, who may assign to the hearing function a more or less primary or coprimary role.

Cochlear nerve preservation is more difficult to achieve due to the lack of specific direct monitoring; brainstem auditory evoked responses are used to continuously monitor the cochlear function intraoperatively, with defined alert criteria (e.g., a reduction of peak III amplitude > 50% reported in the Daniel et al. study). The goal of a meticulous intracapsular resection is to obtain a uniform degree of residual capsule thickness that lies on the cochlear and facial nerves, thereby avoiding nerve damage.

Historically, the hearing preservation rate following microsurgical resection ranged from 0% to 50%, and in their large systematic review of patients with large VSs, Ansari et al. found that hearing preservation after microsurgery was possible in only 28.3%.

The reported functional hearing outcomes should be carefully interpreted in correlation with the duration of the postintervention follow-up period since progressive hearing deterioration over time has been reported in up to 20%–30% of the patients at the 5-year follow-up. A chronic vascular ischemic mechanism has been proposed to explain this phenomenon.

Hearing preservation after SRS for small- to medium-sized VSs was reported in more than 70% of patients with VSs and in up to 90% in those with intracanalicular tumor. In their meta-analysis, Rykaczewski and Zabek pooling data from 28 studies, found a 66% hearing preservation rate after GKRS in 3233 patients during a mean follow-up period of 51.24 months. Yang et al. in a larger systematic review, showed an overall hearing preservation rate of 51% after GKRS in a mean follow-up period of 35 months.

In addition to the previously described vascular component, the cochlear GKRS dose has been shown to be one of the main factors involved with long-term functional hearing outcome. In a larger systematic review, a cochlear hearing preservation rate after GKRS of 51% after GKRS in a mean follow-up period of 35 months.

Our pooled preserved serviceable hearing rate of 59.9% after the combined STR/SRS approach used for large VSs in a short- to medium-term follow-up period represents an encouraging figure and highlights the excellent outcome achieved with this approach.

**Tumor Control**

With a mean follow-up duration of 46 months (range 28–68.8 months) after the combined approach, our analysis showed an overall tumor control rate of 93.9% (range 78%–100%).

The rate of tumor control after microsurgery reported in literature has shown how intimately the recurrence rate is related to the residual tumor volume. The recurrence...
rate of large VSs after total microsurgical removal is reported to be between 4% and 27% \cite{21,25,27,45} and is up to 53% after an STR \cite{13,22,23,39}.

The post-GKRS tumor growth control rate has been reported to be as high as 98% \cite{40} in the literature, and a pooled overall tumor control rate of 92.7% was reported in a recent meta-analysis that included more than 3233 patients. After an STR, 13, 22, 23, 39

In our analysis, 18 patients (7.3%) had tumor progression, 5 of whom were observed and remained stable over time without any further treatment. This rate is comparable to that after a total surgical removal.

Moreover, as stated above, the recurrence rate is related to the residual tumor volume, and a learning curve is necessary to perform an adequate STR, leaving a tumor capsule with the best conformation for optimal SRS planning.

The importance of meticulous preoperative planning and management by a dedicated specialty team cannot be overstated, and the concept of an incomplete resection should in no way encourage a nonspecialty or less experienced surgical team to attempt a surgical treatment.

A specific analysis of predictors of treatment failure was not directly performed in the included studies, and neither patient characteristics nor radiological features were shown to correlate with tumor progression.

**Study Limitations**

The main limitations of this review are related to the observational nature of the available studies, which were mainly based on small cohorts. The methodological drawbacks associated with the retrospective and observational nature of these studies, such as the lack of standardization in the study intervention and combined approach planning, incomplete data, varied follow-up periods, and the diverse definitions of tumor control, characterize the low quality of evidence.

**Conclusions**

The reported data suggest that the combined approach has an excellent clinical and functional outcome while still achieving a tumor control rate comparable to that of total surgical resection. Additional data from larger patient cohorts need to be collated and analyzed for this relatively new combined approach over longer follow-up periods to affirm its clinical utility.

**References**


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

Author Contributions
Conception and design: Starnoni, Daniel, Messerer. Acquisition of data: Starnoni. Analysis and interpretation of data: Starnoni. Drafting the article: Starnoni. Critically revising the article: Daniel, Tuleasca, George, Levivier, Messerer. Reviewed submitted version of manuscript: Daniel, Tuleasca, Levivier, Messerer.

Correspondence
Daniele Starnoni: Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland. daniele.starnoni@chuv.ch.