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# Long-Term Hearing Outcome After Radiosurgery for Vestibular Schwannoma: A Systematic Review and Meta-Analysis

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**BACKGROUND:** Stereotactic radiosurgery (SRS) is one of the main treatment options in the management of small to medium size vestibular schwannomas (VSs), because of high tumor control rate and low cranial nerves morbidity. Series reporting long-term hearing outcome (>3 years) are scarce.

**OBJECTIVE:** To perform a systematic review of the literature and meta-analysis, with the aim of focusing on long-term hearing preservation after SRS.

**METHODS:** Using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, we reviewed articles published between January 1990 and October 2020 and referenced in PubMed or Embase. Inclusion criteria were peer-reviewed clinical study or case series of VSs treated with SRS (single dose), reporting hearing outcome after SRS with a median or mean audiometric follow-up of at least 5 years. Hearing preservation, cranial nerves outcomes, and tumor control were evaluated.

**RESULTS:** Twenty-three studies were included. Hearing preservation was found in 59.4% of cases (median follow-up 6.7 years, 1409 patients). Main favorable prognostic factors were young age, good hearing status, early treatment after diagnosis, small tumor volume, low marginal irradiation dose, and maximal dose to the cochlea. Tumor control was achieved in 96.1%. Facial nerve deficit and trigeminal neuropathy were found in 1.3% and 3.2% of patients, respectively, both significantly higher in Linear Accelerator series than Gamma Knife series ( $P < .05$ ).

**CONCLUSION:** Long-term hearing preservation remains one of the main issues after SRS, with a major impact on health-related quality of life. Our meta-analysis suggests that hearing preservation can be achieved in almost 60% of patients after a median follow-up of 6.7 years, irrespective of the technique.

**KEY WORDS:** Hearing, Prognostic factors, Radiosurgery, Vestibular schwannoma

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Vestibular schwannomas (VSs) are slow growing, intracranial extra-axial, benign tumors that usually develop from the vestibular component of the cochlea-vestibular nerve.<sup>1</sup> They

account for 8% of intracranial tumors.<sup>1</sup> Three main options can be considered in the management of VS depending on the tumor size, clinical presentation, and condition of the patient: wait and scan, stereotactic radiosurgery (SRS), or microsurgical resection. SRS has emerged over the past 30 years as one of the main treatment options in the management of small to medium VS because of its high tumor control rate, low morbidity, and higher induced quality of life compared with surgery.<sup>2-5</sup> In most series and reviews of the literature, tumor

**ABBREVIATIONS:** CK, CyberKnife; GK, Gamma Knife; GR, Gardner Robertson; LINAC, linear accelerator; NF, neurofibromatosis; NS, not specified; PTA, Pure Tone Average; SRS, stereotactic radiosurgery; VS, vestibular schwannoma.

control is reported between 90% and 99%,<sup>6</sup> whereas cranial nerve complications such as facial nerve deficit and trigeminal neuropathy are reported in ranges of 0% to 5% and 1% to 21%, respectively.<sup>6</sup>

Short- and mid-term hearing preservation is generally higher in recent series. The primary reason is the reduction of the marginal prescribed dose<sup>7,8</sup> and hence the subsequent reduction of the maximal dose received by the cochlea.<sup>9-11</sup> For Gamma Knife (GK) SRS, one additional reason may be related to the automation of the procedure, starting with the Perfexion device.<sup>12</sup> However, long-term hearing preservation remains one of the major concerns of SRS treatments. Hearing preservation after SRS is generally reported to be more than 60% at a 3-year follow-up; nevertheless, there are high variations across series.<sup>6,13-20</sup> Moreover, the different hearing scales used and the subjective vs objective evaluations are clouding such assessment. In a recent meta-analysis including 254 publications and 5825 patients, hearing preservation was observed in 57% of the patients<sup>21</sup> at 41 months. Yet, the mean follow-up of the included studies was short and the authors observed impressive variations in hearing preservation rates for patients with VS across series (range: 11%-77%).<sup>21</sup> Another aspect is how SRS compares with natural history in these patients, which remains a debated topic.<sup>22,23</sup> Finally, hearing loss after SRS is deemed to be delayed<sup>4</sup> and series reporting long-term (>5 years) hearing preservation rate are scarce.

We performed a systematic review of the literature and meta-analysis, with the primary aim of focusing on the long-term hearing preservation after SRS and related prognostic factors. The secondary outcomes were the tumor control and the side effects.

## METHODS

### Article Selection and Data Extraction

PubMed and Embase searches were performed for entries between January 1990 and October 2020 using the following query guidelines: (radiosurgery) AND ((vestibular schwannoma) OR (acoustic schwannoma) OR (vestibular neuroma) OR (acoustic neuroma)). Articles published before 1990 were excluded because in most centers, the irradiation doses started to reduce at that period, and then including previous studies would not reflect the current practice. Search filters were set to English and French language articles. The relevance of the retrieved articles was assessed by reading the titles, abstracts, or both. Inclusion criteria required that each article is a peer-reviewed clinical study or a case series of VSs treated by SRS (single dose), irrespective of the device (Linear Accelerator [LINAC]; CyberKnife [CK]; Accuray; GK; Elekta) used. Only series reporting hearing outcome after SRS were included, including at least 10 patients and a median or mean audiometric follow-up of at least 5 years. Studies strictly focusing on patients with neurofibromatosis, on retreatment by radiosurgery, on hypofractionated stereotactic radiosurgery (2-5 fractions) or fractionated radiotherapy, or on combined approaches (radiosurgery performed after planned subtotal resection) were excluded. To avoid overlapping cohorts, when several publications from the same authors or center were eligible for inclusion, we selected the study with the longest audiometric follow-up.

This study was performed in accordance with the published Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.<sup>24</sup> Two separate reviewers (A.B. and C.T.) applied the inclusion criteria to the search results; there were no disagreements. The article selection is exemplified in Figure 1. Relevant biases were assessed by 2 separate reviewers (A.B. and C.T.).

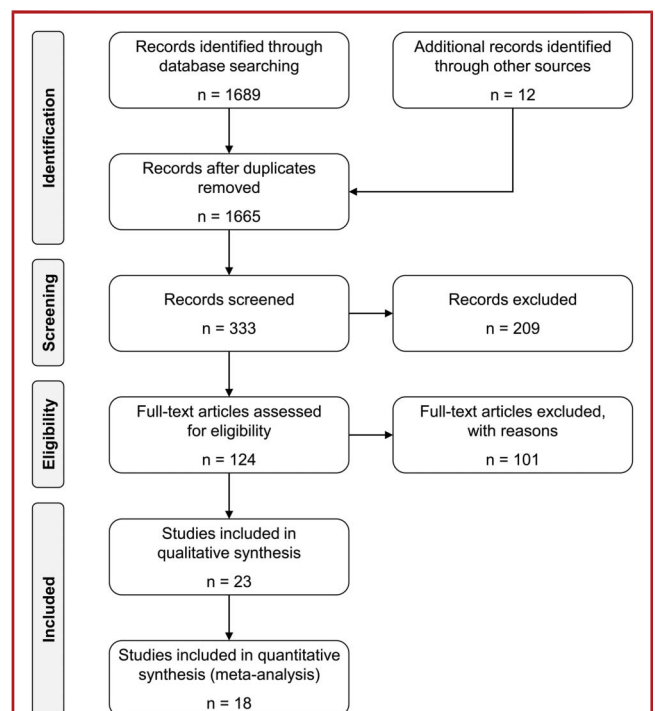
Data extraction was performed as per individual study, while paying special attention to hearing outcome, facial nerve deficit, trigeminal neuropathy, and tumor control.

Serviceable hearing was defined as a Pure Tone Average (PTA) score of 50 dB or less and a speech discrimination score of 50% or more (Gardner Robertson [GR] classes 1 and 2; American Academy of Otolaryngology-Head and Neck Surgery classes A and B).<sup>25,26</sup> The House-Brackmann scale was used to assess facial nerve function.<sup>27</sup> Facial nerve deficit was defined as House-Brackmann grade >II.

### Statistical Analysis

For the meta-analyses, only studies reporting individual data were selected. Because of high variations in study characteristics, a statistical analysis using a binary random-effects model (DerSimonian-Laird method) was performed using OpenMeta[analyst] software (Agency for Healthcare Research and Quality). Weighted summary rates were determined using meta-analytical models. Heterogeneity was tested for each meta-analysis; pooled estimates were obtained for all outcomes.

Results of series concerning hearing outcome, facial nerve deficit, trigeminal neuropathy, and tumor control were compared using a meta-regression with a random effect. *P* values < .05 were considered statistically significant.



**FIGURE 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses<sup>24</sup> flow diagram with study selection details. Studies included in qualitative synthesis correspond to peer-reviewed clinical studies or case series of vestibular Schwannoma treated with SRS (single dose), irrespective of the technique, reporting hearing outcome after SRS with a median or mean audiometric follow-up of at least 5 years. Studies included in quantitative synthesis correspond to the subset of those at least reporting hearing preservation rates; different subsets have been used for meta-analyses focusing on facial nerve deficit, trigeminal neuropathy, and tumor control based on available respective rates. SRS, stereotactic radiosurgery.

**TABLE 1. Hearing Outcome Among the Selected SRS Series and Main Prognostic Factors (u and m Denote Significant Factors According to Univariate and Multivariate Analyses, Respectively)**

| Series<br>(first author, year)  | SRS<br>technique | Patients with<br>serviceable<br>hearing | Median<br>follow-up (y)<br>(range; mean) | Median marginal<br>dose (Gy) (range;<br>mean), Isodose | Median maximal<br>cochlear dose (Gy)<br>(range; mean) | Hearing<br>preservation at<br>last follow-up | Actuarial<br>rates                                   | Prognostic factors   |
|---------------------------------|------------------|---|--|--|---|--|--|--|
| Iwai <sup>28</sup> , 2003       | GK               | 18                                      | 5 (1.5-8; NS)                            | 12 (8-12; NS), NS                                      | NS  | 55.6%  | NS   | NS   |
| Gabert <sup>29</sup> , 2004     | GK               | 175                                     | NS (3-11; 7)                             | NS (9-14; 12.74), 50%                                  | NS (NS; 4.66)   | 60%  | 3 y—60%  | GR 1 (u), tinnitus as first symptom (u), age (u), dose rate (u), sudden deafness (u) |
| Fukuoka <sup>19</sup> , 2009    | GK               | 59                                      | NS (5-NS; NS)                            | 12 (9-15; NS), 50%                                     | NS  | NS   | 3 y—81%<br>5 y—74%<br>6 y—71%                        | NS   |
| Combs <sup>30</sup> , 2010      | LINAC            | 16                                      | 6.3 (0.2-19; NS)                         | 13 (10-20; NS), 80%                                    | NS  | 56.2%  | NS   | Marginal dose ≤13 Gy (u), NF2 (u)  |
| Hsu <sup>31</sup> , 2010        | LINAC            | 32                                      | NS (5-13.6; 8.1)                         | 14 (12-20; NS), 80%                                    | NS  | 87.5%  | NS   | NS   |
| Collen <sup>32</sup> , 2011     | LINAC            | 35                                      | 5.2 (0.5-11.3; NS)                       | 12.5 (11-14; NS), 80%                                  | NS  | NS   | 4 y—82%  | Koos grade (u)   |
| Roos <sup>33</sup> , 2011       | LINAC            | 50                                      | 5.4 (0.8-15.3; NS)                       | NS (12-14; NS), NS                                     | NS  | 38%  | 5 y—50%<br>10 y—23%                                  | NS   |
| Sun <sup>34</sup> , 2012        | GK               | 22                                      | 9.1 (0.7-16.3; NS)                       | 13 (6.0-14.4), 50%                                     | NS  | 81.8%  | 3 y—96%<br>5 y—92%<br>10 y—70%                       | NS   |
| Kim <sup>35</sup> , 2013        | GK               | 60                                      | 5.2 (3-11.7; NS)                         | NS (11.5-13; 12.2), 50%                                | NS (2.7-16.6; 8.2)                                    | 56.7%  | 1 y—70%<br>2 y—63%<br>5 y—55%                        | Marginal dose <13 Gy (u), transient volume expansion >20% (u, m)                     |
| Carlson <sup>36</sup> , 2013    | GK               | 44                                      | 9.3 (NS)                                 | 12 (12-13; 12.1), NS                                   | 4.6 (2.0-8.3; 5.0)                                    | 18.2%  | 1 y—80%<br>3 y—55%<br>5 y—48%<br>7 y—38%<br>10 y—23% | PTA (u, m), GR class (u), brainstem contact (u, m)                                   |
| Anderson <sup>37</sup> , 2014   | LINAC            | 12                                      | 7 (NS)                                   | 12.5 (9.7-16; NS), NS                                  | NS  | NS   | 5 y—60%  | NS   |
| Bir <sup>38</sup> , 2014        | GK               | 82                                      | 5 (0.5-12; NS)                           | NS (12-13; 12), 50%                                    | NS  | NS   | 3 y—90%<br>5 y—83%<br>10 y—58%                       | NS   |
| Boari <sup>39</sup> , 2014      | GK               | 96                                      | 5.8 (3-13.1; 6.3)                        | 13 (11-15; NS), 50%                                    | NS  | 49%  | 1 y—80%<br>3 y—55%<br>5 y—40%                        | Age <55 y old (m)  |
| Tveiten <sup>40</sup> , 2015    | GK               | 97                                      | NS (NS; 7.7)                             | NS   | NS  | 40.2%  | NS   | NS   |
| Ellenbogen <sup>41</sup> , 2015 | LINAC            | 10                                      | 5.8 (1.4-9.2; NS)                        | 12.5 (NS), 80%   | NS  | 50%  | NS   | NS   |

TABLE 1. Continued.

| Series<br>(first author, year) | SRS<br>technique | Patients with<br>serviceable<br>hearing | Median<br>follow-up (y)<br>(range; mean) | Median marginal<br>dose (Gy) (range;<br>mean), Isodose | Median maximal<br>cochlear dose (Gy)<br>(range; mean) | Hearing<br>preservation at<br>last follow-up | Actuarial<br>rates   | Prognostic factors   |
|--------------------------------|------------------|---|--|--|---|--|--|--|
| Akpınar <sup>42</sup> , 2016   | GK               | 88                                      | 6.3 (1-14.1; NS)                         | 12.5 (11.5-13; NS), NS                                 | NS  | NS   | Early/late<br>treatment<br>1 y—96%/87%<br>3 y—93%/73%<br>5 y—88%/55%<br>10 y—64%/55% | Early treatment (<2 y after<br>diagnosis), PTA <20 dB (m)  |
| Klijn <sup>43</sup> , 2016     | GK               | 71                                      | 5.1 (4.0-7.0; NS)                        | NS (11-13; NS), 62%                                    | NS  | 60.6%  | 3 y—65%<br>5 y—42%   | NS   |
| Pan <sup>44</sup> , 2017       | GK               | 64                                      | NS (NS; 6.4)                             | 12 (NS; 12), 50%                                       | NS (NS; 3.3)  | 81.2%  | NS   | Tumor morphology (u, m), length<br>of tumor in IAC (u), width of<br>tumor in IAC (u), brainstem<br>compression (u), 4th ventricle<br>compression (u), cochlear dose<br>(u), dose to the semicircular<br>canal (u), dose and 10 Gy<br>volume in the brainstem (u) |
| Lin <sup>45</sup> , 2017       | GK               | 100                                     | 6.5 (3-10; 5.8)                          | 12 (12-13; 12.1), 50%                                  | 6.1 (1.3-13; 5.9)                                     | 61%  | 1 y—89%<br>3 y—68%<br>5 y—63%  | Mean cochlear dose <4 Gy (u),<br>tumor control (u)   |
| Frischer <sup>46</sup> , 2018  | GK               | 132                                     | 5.1 (2-20.7; NS)                         | 12 (5-17; NS), 50%                                     | NS  | 55.3%  | 5 y—53%<br>10 y—34%<br>15 y—34%  | GR class (u, m), Koos grade (u),<br>median cochlear dose (u, m),<br>age (u)  |
| Hasegawa <sup>47</sup> , 2018  | GK               | 92                                      | 8.8 (3-21.8; NS)                         | 12 (10.4-16.8), 50%                                    | 4 (1.6-10.5; NS)                                      | 53.3%  | 3 y—66%<br>5 y—57%<br>8 y—47%<br>10 y—44%  | Fundus obliteration (u), distance<br>from fundus to the tumor end<br>(u), difference between bilateral<br>PTA (u), 4-mm collimator to the<br>intracanalicular portion (u),<br>mean cochlear dose <5 Gy (u,<br>m), PTA <30 dB (u, m)                              |
| Johnson <sup>48</sup> , 2019   | GK               | 307                                     | 7.6 (1-23; NS)                           | 12.5 (12-15; NS), 50%                                  | NS  | 60.6%  | 3 y—77.8%<br>5 y—68.8%<br>10 y—51.8%   | Young age (u, m), GRI (u, m), tumor<br>volume <1.2 cm <sup>3</sup> (u, m)  |
| Anselmo <sup>49</sup> , 2020   | LINAC            | 23                                      | 12 (2-16; NS)                            | 16.5 (13-20; NS), NS                                   | NS  | 91.3%  | NS   | NS   |

GK, Gamma Knife; GR, Gardner Robertson; LINAC, linear accelerator; NF, neurofibromatosis; NS, not specified; PTA, Pure Tone Average.

Median follow-up, marginal dose, and maximal cochlear dose refer to the entire cohort reported, which may include patients with nonserviceable hearing. Serviceable hearing denotes a pure tone average (PTA) score of 50 dB or less and a speech discrimination score of 50% or more (GR classes 1 and 2; AAO-HNS classes A and B). No studies using CyberKnife stereotactic radiosurgery met the inclusion criteria.

**TABLE 2. Study Criteria, Facial Nerve Palsy, Trigeminal Neuropathy, and Tumor Control Among the Selected SRS Series**

| Series (first author, year)     | SRS technique | Patients | Study criteria   | Median tumor volume (cm <sup>3</sup> ) (range; mean) | New facial nerve deficit | New trigeminal neuropathy | Tumor control |
|---------------------------------|---------------|----------|--|--|--------------------------|---------------------------|---------------|
| Iwai <sup>28</sup> , 2003       | GK            | 51       | Marginal dose ≤12 Gy   | 3.6 (0.7-24.9; NS)                                   | 0%                       | 3.9%                      | 96.1%         |
| Gabert <sup>29</sup> , 2004     | GK            | 175      | Sporadic VS, serviceable hearing at SRS, follow-up >36 mo      | NS   | NS                       | NS                        | NS            |
| Fukuoka <sup>19</sup> , 2009    | GK            | 152      | Follow-up >60 mo   | 2.0 (0.1-18.7; NS)                                   | 1.3%                     | 4.6%                      | NS            |
| Combs <sup>30</sup> , 2010      | LINAC         | 30       | NS   | NS   | 16.7%                    | 6.7%                      | 93.3%         |
| Hsu <sup>31</sup> , 2010        | LINAC         | 75       | Sporadic VS, follow-up ≥60 mo                                  | 1.5 (0.1-23.7; NS)                                   | 8%                       | 0%                        | 92%           |
| Collen <sup>32</sup> , 2011     | LINAC         | 78       | NS   | NS (0.1-9.5; 1.7)                                    | 15.9%                    | 5.6%                      | 93.6%         |
| Roos <sup>33</sup> , 2011       | LINAC         | 102      | NS   | NS   | 8.8%                     | 14.7%                     | 97.6%         |
| Sun <sup>34</sup> , 2012        | GK            | 190      | Sporadic VS, marginal dose ≤14 Gy                              | 3.6 (0.3-27.3; NS)                                   | 1.1%                     | 2.6%                      | 89.5%         |
| Kim <sup>35</sup> , 2013        | GK            | 60       | Sporadic intracanalicular VS, serviceable hearing at SRS       | NS (0.03-1.00; 0.34)                                 | NS                       | NS                        | 100%          |
| Carlson <sup>36</sup> , 2013    | GK            | 182      | Marginal dose ≤12-13 Gy  | 0.7 (0.2-12; 1.7)                                    | NS                       | NS                        | 97.3%         |
| Anderson <sup>37</sup> , 2014   | LINAC         | 48       | NS   | 0.66 (NS)  | 2.1%                     | 12.5%                     | NS            |
| Bir <sup>38</sup> , 2014        | GK            | 82       | NS   | NS (0.2-16; 3.24)                                    | 0%                       | 3.7%                      | 97.6%         |
| Boari <sup>39</sup> , 2014      | GK            | 379      | GK as primary treatment, sporadic VS, follow-up ≥36 mo         | 1.2 (0.01-14.3; 1.94)                                | 1.1%                     | 1.8%                      | 97.1%         |
| Tveiten <sup>40</sup> , 2015    | GK            | 247      | Maximal tumor diameter ≤3 cm                                   | NS   | NS                       | NS                        | NS            |
| Ellenbogen <sup>41</sup> , 2015 | LINAC         | 50       | NS   | 2.4 (0.24-10.59; NS)                                 | 4%                       | 4%                        | 96%           |
| Akpınar <sup>42</sup> , 2016    | GK            | 88       | Serviceable hearing at SRS with no subjective loss             | 0.72 (0.11-12.80; NS)                                | 0%                       | NS                        | 100%          |
| Klijn <sup>43</sup> , 2016      | GK            | 420      | GK as primary treatment, sporadic VS                           | 1.4 (NS)   | 0.7%                     | 3.1%                      | 89.3%         |
| Pan <sup>44</sup> , 2017        | GK            | 93       | GK as primary treatment, marginal dose 12 Gy, follow-up ≥60 mo | 3.14 (NS)  | 0%                       | NS                        | NS            |
| Lin <sup>45</sup> , 2017        | GK            | 100      | Serviceable hearing at SRS, marginal dose 12-13 Gy             | NS   | NS                       | NS                        | 85%           |
| Frischer <sup>46</sup> , 2018   | GK            | 498      | Sporadic VS, follow-up ≥12 mo                                  | NS (0.1-19.6; NS)                                    | 1%                       | 0%                        | 98.8%         |
| Hasegawa <sup>47</sup> , 2018   | GK            | 92       | Serviceable hearing at SRS                                     | 1.5 (0.1-14.5; NS)                                   | 0%                       | 0%                        | 98.9%         |
| Johnson <sup>48</sup> , 2019    | GK            | 307      | Serviceable hearing at SRS                                     | 0.7 (0.02-16.7; NS)                                  | NS                       | NS                        | 94.8%         |
| Anselmo <sup>49</sup> , 2020    | LINAC         | 48       | NS   | 1.7 (0.09-7.4; NS)                                   | 8.3%                     | 22.9%                     | 100%          |

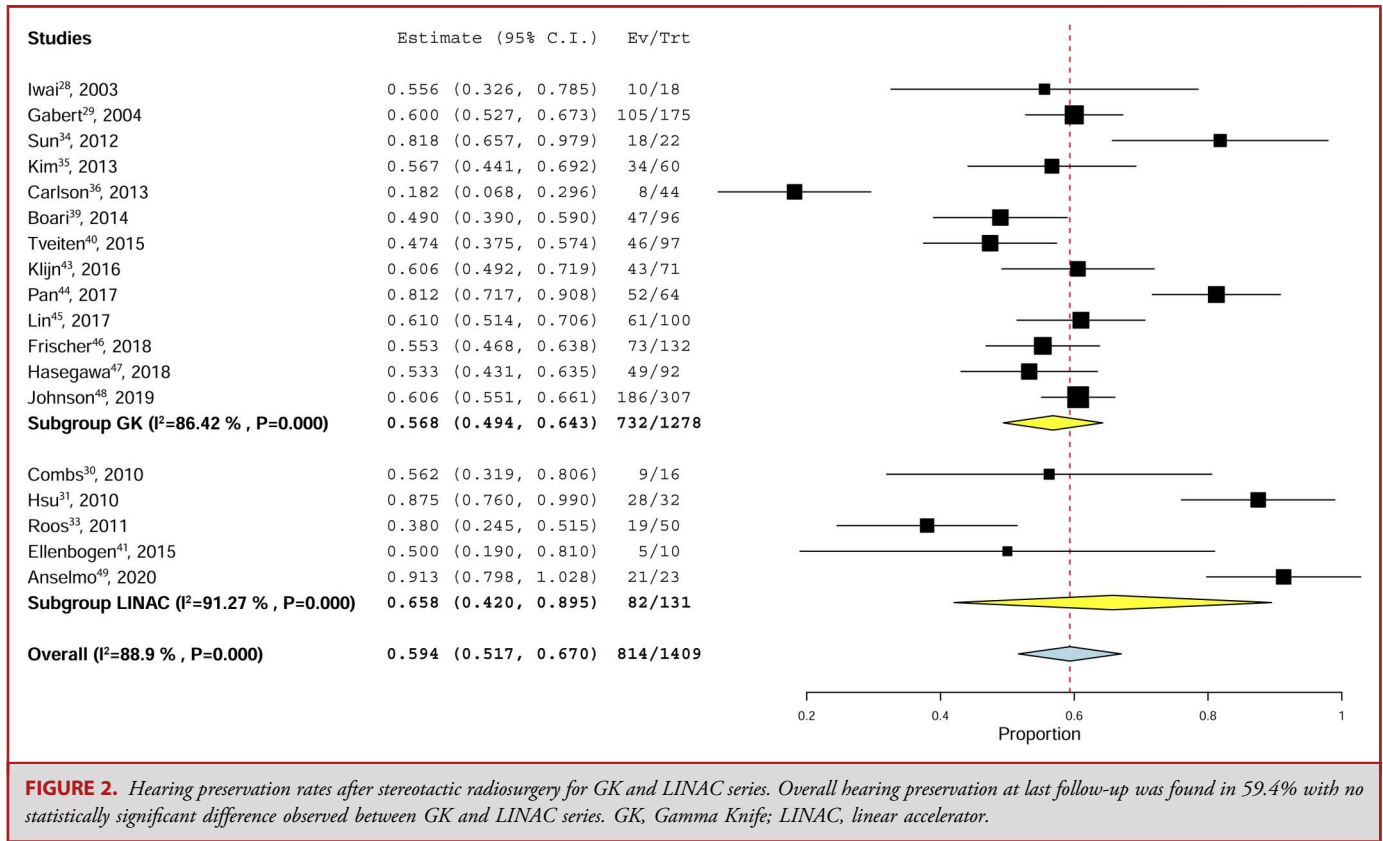
GK, Gamma Knife; LINAC, linear accelerator; NS, not specified; SRS, stereotactic radiosurgery; VS, vestibular schwannomas.

Facial nerve deficit denotes a House-Brackmann grade > II. No studies using CyberKnife stereotactic radiosurgery met the inclusion criteria.

## RESULTS

Twenty-three studies<sup>19,28-49</sup> were included in this systematic review (3547 patients of whom 1685—47.5%—had serviceable

hearing at the time of SRS). Sixteen studies reported the results of GK SRS,<sup>19,28,29,34-36,38-40,42-48</sup> and 7 studies reported the results of LINAC SRS.<sup>30-33,37,41,49</sup> No studies using CK SRS met the inclusion criteria. The detailed study characteristics are collated in Tables 1 and 2.



## Dosimetric Parameters

The median marginal dose prescribed in GK and LINAC series was 12.3 Gy at 50% isodose (range: 5-17 Gy) and 13.5 Gy at 80% isodose (range: 10-20 Gy), respectively. Median tumor volumes in GK and LINAC series were 1.9 cm<sup>3</sup> (range: 0.01-27.3 cm<sup>3</sup>) and 1.6 cm<sup>3</sup> (range: 0.09-23.7 cm<sup>3</sup>), respectively. Individual cochlear dose data were lacking for the analysis, and only range and mean doses were reported in 6/18 studies (30%).

## Hearing Outcome

Overall hearing preservation was found in 59.4% (range: 51.7%-67.0%,  $I^2 = 88.9\%$ ,  $p$  heterogeneity  $P < .001$ ,  $P < .001$ ; Figure 2) with a median follow-up of 6.7 years (range: .2-23 years;  $n = 1409$  patients). Hearing preservation in GK series was found in 56.8% (range: 49.4%-64.3%,  $I^2 = 86.42\%$ ,  $p$  heterogeneity  $P < .001$ ,  $P < .001$ ; Figure 2) with a median follow-up of 6.6 years (range: .5-23 years; 1278 patients). Hearing preservation in LINAC series was found in 65.8% (range: 42.0%-89.5%,  $I^2 = 91.27\%$ ,  $p$  heterogeneity  $P < .001$ ,  $P < .001$ ; Figure 2) with a median follow-up of 7.0 years (range: .2-19 years; 131 patients). There was no statistically significant difference observed between GK and LINAC series ( $P = .28$ ).

We also collated the main prognostic factors of long-term hearing preservation after SRS (Table 1). Considering the clinical presentation, the main prognostic factors were young age,<sup>29,39,48</sup> tinnitus as first

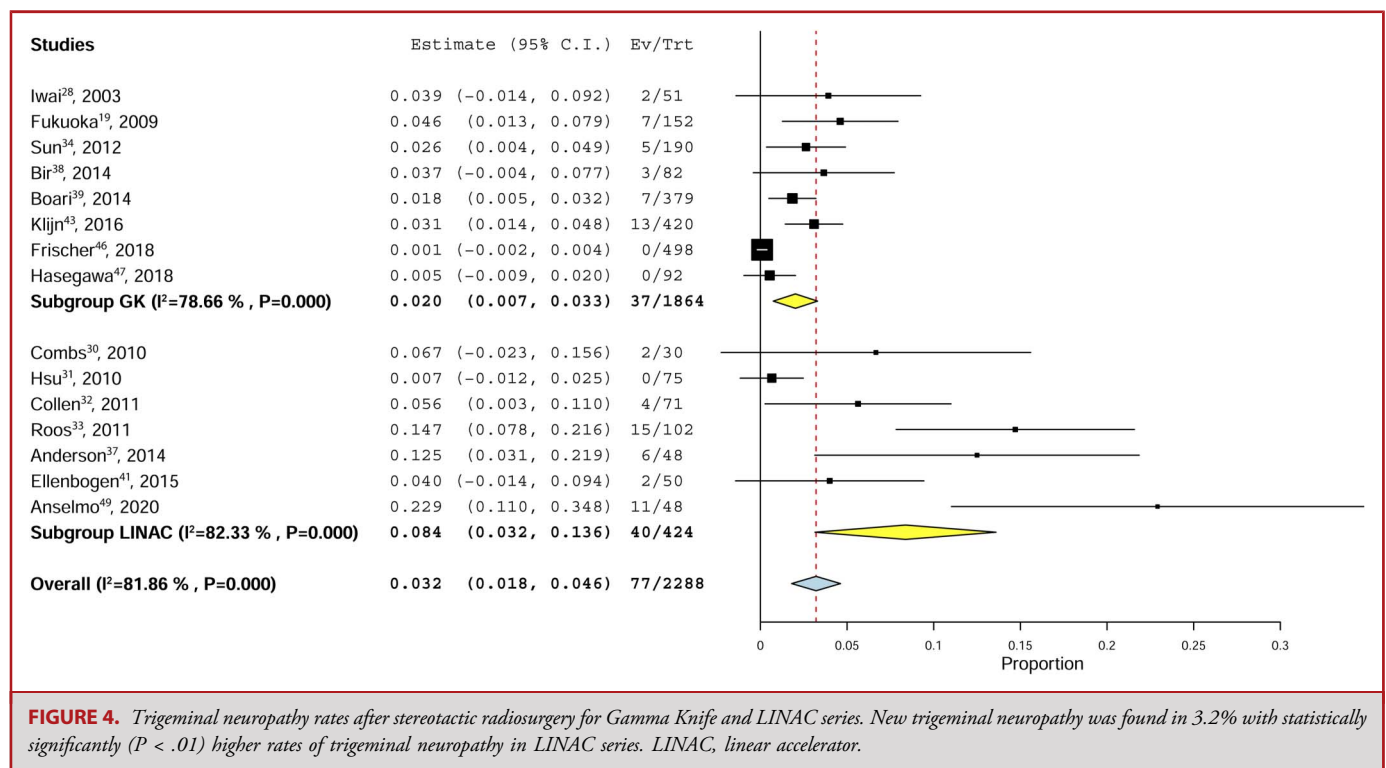
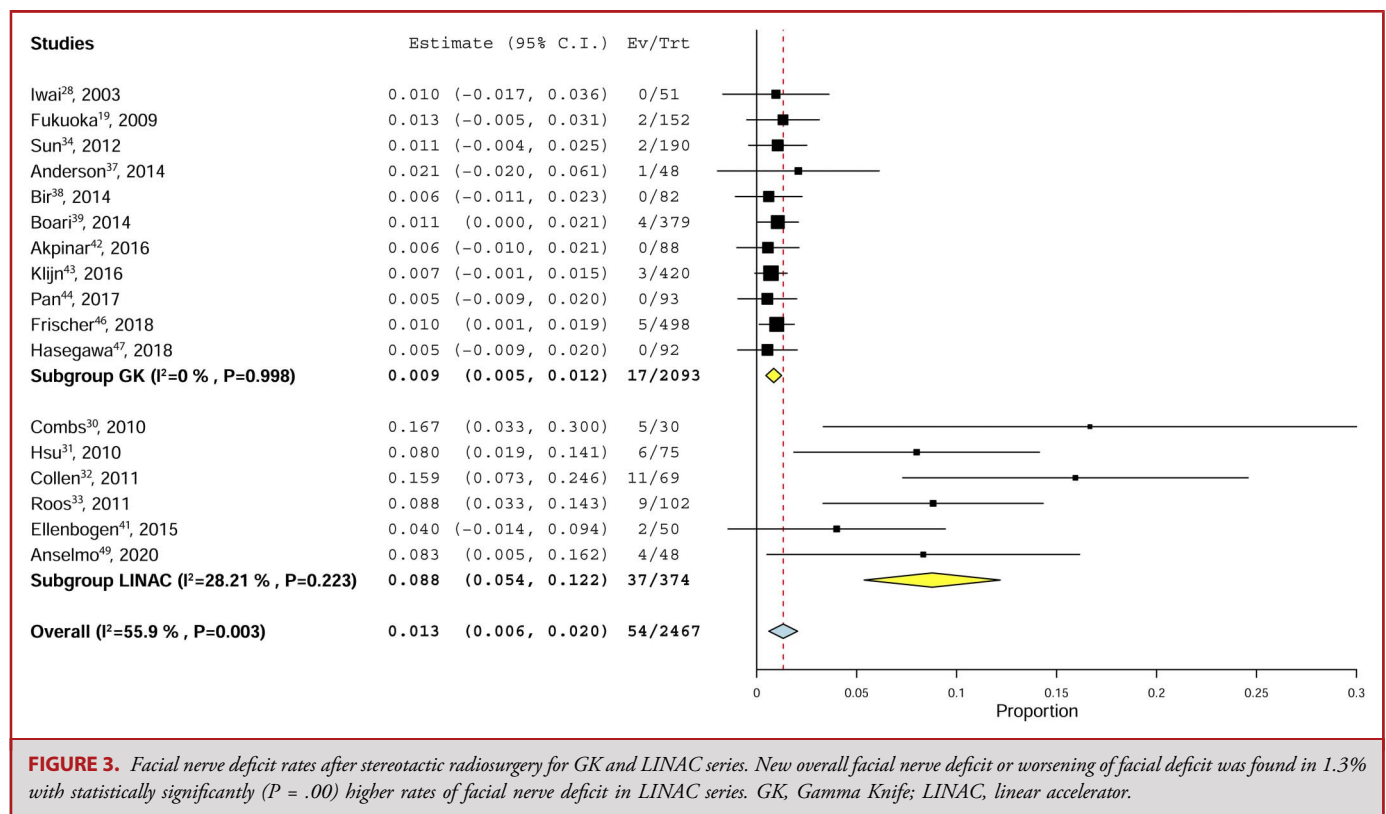
symptom,<sup>29</sup> small difference between bilateral PTA scores,<sup>47</sup> good hearing status at SRS (GR class 1; PTA  $\leq 20$ -30 dB),<sup>29,33,36,42,46-48</sup> and early treatment (less than 2 years after diagnosis).<sup>42</sup> Considering the tumor characteristics, the main prognostic factors were sporadic VS,<sup>30</sup> small tumor volume ( $< 1.2$  cm<sup>3</sup>),<sup>48</sup> Koos I grading,<sup>31,44,46</sup> absence of brainstem compression,<sup>36,44</sup> absence of fundus obliteration by the tumor, and long distance from fundus to the tumor end. Considering the SRS treatment modalities, the main prognostic factors were low marginal dose ( $< 13$  Gy for GK series) and low maximal dose to the cochlea ( $< 4$ -5 Gy).<sup>29,44-47</sup>

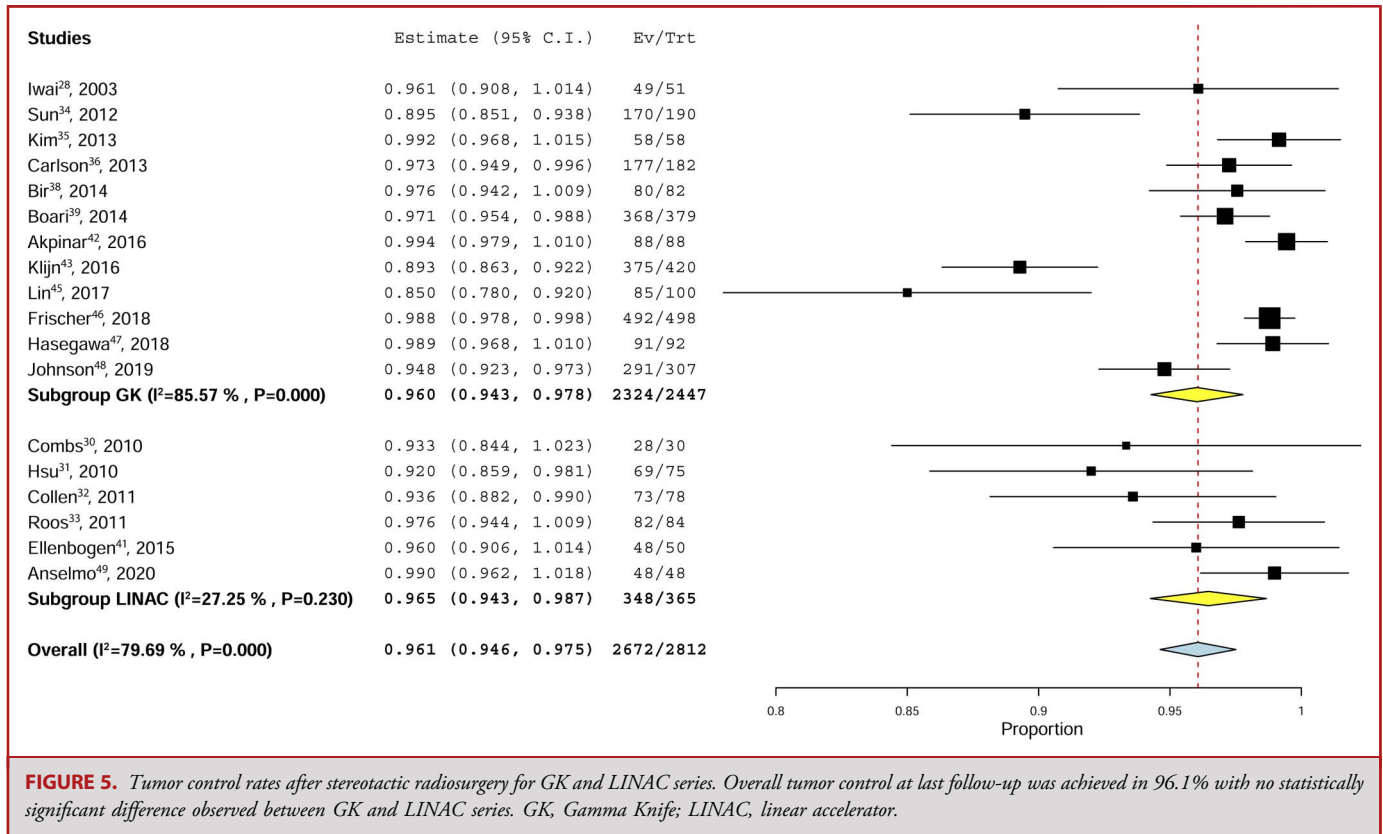
## Facial and Trigeminal Outcomes

New overall facial nerve deficit or worsening of facial deficit (House-Brackmann  $> II$ ) was found in 1.3% (range: .6%-2.0%,  $I^2 = 55.9\%$ ,  $p$  heterogeneity  $P = .003$ ,  $P < .01$ ; Figure 3). New facial nerve deficit or worsening of facial deficit in GK series was found in .9% (range: .5%-1.2%,  $I^2 = 0.0\%$ ,  $p$  heterogeneity  $P = .99$ ,  $P < .001$ ; Figure 3). New facial nerve deficit or worsening of facial deficit in LINAC series was found in 8.8% (range: 5.4%-12.2%,  $I^2 = 28.21\%$ ,  $p$  heterogeneity  $P = .22$ ,  $P < .01$ ; Figure 3). The difference observed between GK and LINAC series was statistically significant ( $P = .00$ ), with higher rates of facial nerve deficit in LINAC series.

New trigeminal neuropathy (decrease in facial sensation or development of new pain) was found in 3.2% (range: 1.8%-4.6%,







**FIGURE 5.** Tumor control rates after stereotactic radiosurgery for GK and LINAC series. Overall tumor control at last follow-up was achieved in 96.1% with no statistically significant difference observed between GK and LINAC series. GK, Gamma Knife; LINAC, linear accelerator.

$I^2 = 81.86\%$ ,  $p$  heterogeneity  $P = .00$ ,  $P < .001$ ; Figure 4). New trigeminal neuropathy in GK series was found in 2.0% (range .7%-3.3%,  $I^2 = 78.66\%$ ,  $p$  heterogeneity  $P = .00$ ,  $P < .001$ ; Figure 4). New trigeminal neuropathy in LINAC series was found in 8.4% (range: 3.2%-13.6%,  $I^2 = 82.33\%$ ,  $p$  heterogeneity  $P = .00$ ,  $P < .01$ ; Figure 4). The difference observed between GK and LINAC series was statistically significant ( $P < .01$ ), with higher rates of trigeminal neuropathy in LINAC series.

### Tumor Control

The definition of tumor progression varied across studies: largest tumor diameter increased by  $>20\%$ ,<sup>46</sup> a tumor volume increase of 10% or a  $\geq 2$  mm growth in the largest diameter,<sup>34</sup> volume increase of  $\geq 20\%$ <sup>35</sup> or 25%,<sup>47</sup> 1 mm of tumor growth in 2 directions or 2 mm of tumor growth in 1 direction,<sup>28</sup> a minimum diameter increase of 2 mm in any direction,<sup>43</sup> need for further therapy,<sup>37</sup> and tumor growth in excess of 5 mm in any axis or 25% compared with any baseline dimension.<sup>37</sup> It was sometimes not clearly specified.<sup>30,32,39,41,44,45,48,49</sup> To allow studies comparison, we defined tumor control as no need for further treatment (surgical resection or second SRS). Overall tumor control at last follow-up was achieved in 96.1% (range: 94.6%-97.5%,  $I^2 = 79.69\%$ ,  $p$  heterogeneity  $P = .000$ ,  $P < .001$ ; Figure 5). Tumor control in GK series was achieved in 96.0% (range: 94.3%-98.7%,  $I^2 = 85.57\%$ ,  $p$  heterogeneity

$P = .00$ ,  $P < .001$ ; Figure 5). Tumor control in LINAC series was achieved in 96.5% (range: 94.3%-98.7%,  $I^2 = 27.25\%$ ,  $p$  heterogeneity  $P = .230$ ,  $P < .001$ ; Figure 5). There was no statistically significant difference observed between GK and LINAC series ( $P = .98$ ).

### Tinnitus and Vestibular Dysfunction

Data on tinnitus and vestibular dysfunction were scarcely reported in the selected studies. Klijn et al,<sup>32</sup> Frischer et al,<sup>46</sup> and Collen et al<sup>43</sup> reported new or temporary increased symptoms of tinnitus in 13.2%-30% of the patients, and new or increased symptoms of vertigo in 7%-30%. This increase typically occurred 6 months after SRS.<sup>46</sup> On the contrary, some authors reported improvements in pre-SRS symptoms for 38% to 62.5% of patients.<sup>34,39,49</sup>

### Risk of Bias

The patients included in the series vary on several criteria (Table 2): sporadic<sup>29,31,35,39,46</sup> vs sporadic + neurofibromatosis<sup>33</sup> patients, all VSs vs intracranial VS,<sup>35</sup> marginal dose.<sup>28,29,34,36,44,45</sup> The number of patients per study ranges from 10 to 307. Finally, the strategy varies among studies, with some teams proposing upfront SRS,<sup>29,44</sup> some leaving the treatment choice to the patient,<sup>15</sup> and some waiting for clinical deterioration or radiological progression.<sup>30,41,43</sup>



## DISCUSSION

### General Interpretation

In the present meta-analysis, overall hearing preservation after SRS for VS was found in 59.4% after a median follow-up of 6.7 years. Overall tumor control at last follow-up was achieved in 96.1% of patients. Overall new facial nerve deficit or worsening of facial deficit was found in 1.3%, with significantly higher rates of facial nerve deficit in LINAC series. Overall new trigeminal neuropathy was found in 3.2% of patients, with significantly higher rates of trigeminal neuropathy in LINAC series. Although the primary aim of the review was to focus on the long-term hearing outcome, evaluating tumor control, facial nerve deficit, and trigeminal neuropathy rates of these cohorts remains mandatory to ensure that the reported hearing preservation rates reflect everyday practice. Regarding the increased toxicity of LINAC vs GK, the same finding was recently reported in a meta-analysis by Guadix et al<sup>50</sup> for trigeminal neuropathy. Yet, for facial nerve deficit, this observation was not established before.

The optimal timing of SRS after initial diagnosis is still debated in the literature, with some teams advocating for early treatment and some waiting for clinical deterioration before treatment. In their series, Carlson et al<sup>36</sup> reported the lowest rate of hearing preservation among all selected series (18.2%). One reason of such a low preservation rate may be related to a very long follow-up (9.3 years). Yet, if we compare these results with the results of our meta-analysis, there is a major difference in hearing preservation rate. One reason of such a discrepancy may be the timing of SRS, with SRS either proposed upfront or in the case of audiometric or clinical deterioration. Akpınar et al<sup>42</sup> specifically addressed this question and showed that early SRS improves hearing preservation. This observation has been corroborated by multiple studies reporting a higher chance of long-term hearing preservation obtained for young patients, GR class 1, not complaining of hearing deterioration (GR class 1-A<sup>51</sup>), and Koos grade I.<sup>23,29,52,53</sup>

Two other main strategies can be proposed in the management of VS. Considering the wait and scan strategy, the probability of keeping serviceable hearing likely diminishes with time and in the case of tumor progression.<sup>54</sup> In a recent meta-analysis including 15 series and 2142 patients initially observed, the probability of keeping serviceable hearing at a 5-year follow-up was evaluated to be 50%.<sup>54</sup> The main prognostic factors in the wait and scan strategy are initial hearing status, initial tumor volume, and tumor growth.<sup>55</sup> Hearing preservation after microsurgical resection varies across series. These results mostly depend on the microsurgical approach<sup>56</sup> (retrosigmoid, translabyrinthine, or middle cranial fossa), the amount of resection planned,<sup>57</sup> the preoperative hearing status, and the initial tumor growth.<sup>58</sup> In a recent meta-analysis including 10 articles and 109 patients treated by surgical resection, hearing preservation was reported in 78.9% at a 5-year follow-up.<sup>59</sup> Yet, the numbers of studies and patients included in this analysis are extremely low. Conversely, in most series, reported hearing preservation at last follow-up ranges from 20% to 60%.<sup>40,56</sup> Although most authors have shown that hearing outcome is obtained in the

immediate postoperative period,<sup>56,59,60</sup> some advocate for long-term hearing deterioration.<sup>61-63</sup> The exact mechanism of this deterioration is not completely understood and could be linked to microscopic tumor recurrence, development of endolymphatic hydrops, or toxicity because of the use of muscle in packing the intra-auricular canal,<sup>59</sup> among other possible explanations. No longer-term studies exist, preventing comparative analyses between SRS and surgery concerning hearing preservation.

### Limitations of the Review Process

This meta-analysis holds several inherent limitations, some of which might have also influenced the reported results. First, only English and French languages articles were searched for because most articles on VS treated by SRS, and especially those with the largest cohorts, were written in these languages. Second, the patients included in the series vary on several criteria, leading to a risk of bias. Third, the timing of SRS varies on centers. Fourth, the definition of tumor progression and tumor control varies across studies. To allow studies comparison, we defined tumor control as no need for further treatment. Yet, this definition may underestimate the rate of failure because some patients may be lost to follow-up before having a second treatment but still have a major increase of their tumor volume. Finally, in some studies included in this meta-analysis, the number of patients with serviceable hearing at SRS was low. Overall, this disparity in the included studies engenders high heterogeneity among the pooled data, limiting the prediction quality of such analysis. Unfortunately, there are many sources of heterogeneity, which cannot be controlled; these are linked to the variety of practices among centers and are inherent to the type of article published (retrospective case series).

### Limitations of Evidence

There might be a selection bias in the reported series concerning hearing preservation. Indeed, it would be of interest to know, for each series, the number of patients lost to follow-up of all those who started with serviceable hearing. Patients with post-SRS unserviceable hearing might not have continued to seek additional follow-up, potentially leading to an underestimation of hearing loss.<sup>48</sup> Unfortunately, this information is scarcely available.<sup>36,42</sup> To assess the evolution of hearing preservation over time, extraction of raw individual patients' data from published Kaplan–Meier estimators in the selected series might have allowed us to calculate pooled actuarial rates. Yet, only 11 GK series<sup>19,34-36,38,39,43,45-48</sup> and 3 LINAC<sup>30,33,37</sup> series reported Kaplan–Meier estimators, representing 911 patients of 1685 in the selected series (54%). Moreover, only 3 GK series<sup>35,36,47</sup> and 1 LINAC series<sup>33</sup> reported the number at risk at each landmark, which is required for meta-analysis of time-dependent variables derived from Kaplan–Meier estimators.<sup>64,65</sup>

Handicap caused by tinnitus has received far less attention than hearing or facial nerve deficit.<sup>40</sup> In our meta-analysis, only 3 studies reported data on tinnitus. Most studies reported increased symptoms in the first few months after SRS that tended to disappear on the longer term.<sup>32,39,43,46,49</sup> Tveiten et al<sup>40</sup> showed

that patient-reported tinnitus and hearing handicap were strongly associated. Data on tinnitus are scarcely reported in the literature on VS treated by SRS. Yet, it has been shown that tinnitus had a negative impact on quality of life.<sup>66,67</sup> Sughrue et al<sup>68</sup> evaluated the risk of induced tinnitus as <1%. The variability of the results across the selected series of their meta-analysis might be linked to the post-SRS timing of the analysis.

Vestibular dysfunctions such as dizziness and vertigo are also scarcely reported. Yet, vestibular dysfunction has been shown to have a high impact on quality of life.<sup>66,69-71</sup> We had observed in a previous study that SRS could improve gait control, yet longer-term data were needed.<sup>72</sup> The same finding was reported by Anselmo, Boari, and Sun et al<sup>34,39,49</sup> On the contrary, some authors reported induced or increased vestibular dysfunction in the first few months after SRS,<sup>32,46</sup> which tends to reduce on the longer term. In their meta-analysis, Sughrue et al<sup>68</sup> evaluated the risk of vestibular dysfunction after SRS at 1.1% to 1.8% depending on the marginal dose.

Although tinnitus and vestibular dysfunction have a high impact on quality of life, the rate of induced deficit seems low and acceptable for the patient.

## Implications

The primary aim in the management of VS is tumor control. The secondary aim is cranial nerves preservation, in particular, for the cochlear, facial, and trigeminal ones. Although tumor control is achieved in a majority of cases, hearing preservation remains one of the major issues with a high impact on health-related quality of life.<sup>73,74</sup> Hearing preservation after SRS is generally reported to be more than 60% at a 3-year follow-up,<sup>6,13-20</sup> yet longer-term data are scarce. This meta-analysis suggests that the same result is achieved on the longer term.

## CONCLUSION

Hearing status has a major impact on health-related quality of life in patients treated with SRS for small- to medium-size VS. Although multiple publications have reported hearing outcome at 3 years after SRS, long-term data remain scarce. In the present meta-analysis, we have shown that serviceable hearing could be preserved for at least 6 years in almost 60% of patients undergoing SRS for VS. The main prognostic factors were young age, the absence of subjective hearing loss, good hearing status at SRS, early treatment, small tumor volume, low marginal dose, and low maximal dose to the cochlea. Hearing preservation rates at 10 to 20 years after SRS remain unknown, and long-term individual prognoses still have to be determined. Trigeminal neuropathy and facial nerve deficit were significantly higher in LINAC series compared with GK series. CK series did not report long-term outcomes.

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This image was generated using Stable Diffusion v1.5 and the Automatic1111 user interface with the prompt “doctor speaking with a patient in the office”, Euler A sampling, a step count of 60, the ERSGAN upscaler, and a CFG = 7 on a 40Gb nVidia A100 GPU. Note the strange hands for both doctors, the bizarre stethoscope head for the physician on the left, and the strange stethoscope ears mysteriously appearing in the crook of the arm of the physician on the right. There are additional hands on the right of the image, perhaps from someone out of field, as well as clipping artifacts with the doctor on the left and the mysterious gentleman behind him – who is in front of whom? Generative diffusion models have a well documented difficulty with generating hands, making the bizarre hands a common sign of AI generated images. Interestingly more advanced models seem to be good at hiding hands (everyone in the image has their hands behind their back), and in all cases strange hands can be fixed via additional steps of in-painting and user editing of the initial generated images. The lack of racial and gender diversity in the photo (all white males) further suggests a possible bias to the model’s associations with the word surgeons. The indiscriminate training of these models on large datasets scraped from the internet predisposes them to acquiring biases that can be difficult to catch without careful analysis.