Critical Review

The Effect of Cochlear Dose on Hearing Preservation After Low-Dose Stereotactic Radiosurgery for Vestibular Schwannomas: A Systematic Review

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Abstract

Purpose: Despite excellent tumor control after stereotactic radiosurgery (SRS) for vestibular schwannoma (VS), the hearing preservation rate remains unsatisfactorily low. Although many factors have been associated with hearing loss, the dose to cochlea has gained more interest in recent years. However, studies investigating the relation between cochlear dose and hearing outcomes have produced inconsistent results. The purpose of this work is to systematically review the literature and critically analyze the studies that investigated the correlation between cochlear dose and hearing loss.

Methods and Materials: A literature search of Ovid MEDLINE, Embase, and Scopus was performed. Studies were included if the SRS dose used was 11 to 14 Gy and included adult patients with sporadic VS, initially serviceable hearing, and at least 24 months of mean or median follow-up.

Results: Twenty-one cohort studies and 1 case-control study were eligible for inclusion, and none were considered to be truly prospective. There was substantial heterogeneity between studies in terms of baseline hearing status, cochlear dosimetry, definition and reporting of hearing outcome, and duration of follow-up, limiting comparison between studies and precluding formal meta-analysis. Eleven studies showed a statistically significant correlation between cochlear dose and hearing outcome, but there was considerable variation in the reported cochlear dose parameter that predicted hearing outcome and whether it was an independent predictor. The definition of hearing outcome and whether the outcome variable is continuous or dichotomous have a bearing on the reported correlation between cochlear dose and hearing outcome.

Conclusions: Whether cochlear dose is a predictor of hearing preservation after SRS for VS could not be unequivocally determined. Future studies should use consistent cochlear dosimetry and hearing outcomes for reliable assessment. In the meantime, based on currently available data, a practical approach will be to aim for a mean cochlear dose <4 to 6 Gy without compromising tumor dose.

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Introduction

Stereotactic radiosurgery (SRS) is the mainstay of nonsurgical treatment for vestibular schwannoma (VS). Leksell pioneered the SRS technique in the 1960s using a Cobalt 60 Gamma Unit, which became known as the Gamma Knife. Nowadays, SRS can also be performed using linear accelerator, CyberKnife, or proton beam therapy units. Regardless of the treatment device, the common attributes of SRS include stereotactic localization of the tumor, delivery of a highly precise single dose of radiation and a steep dose fall off beyond the target volume, reducing the dose to surrounding structures. For VS smaller than 3 cm, SRS has become the preferred treatment due to the lower morbidity compared with surgical treatment and comparable long-term tumor control.\(^2\)\(^-\)\(^4\)

The current standard for VS is to use a marginal tumor dose of 12 to 14 Gy, lower than the doses used previously, to reduce treatment-related toxicity.\(^5\)-\(^7\) Although long-term tumor control is comparable to that with higher doses, the lower doses are associated with better preservation of facial nerve function\(^8\),\(^9\) and hearing.\(^10\),\(^11\) Long-term hearing preservation, however, remains disappointingly low (23%-64%).\(^12\),\(^13\),\(^14\),\(^15\)

Although many mechanisms have been postulated, the pathogenesis of hearing loss is currently poorly understood.\(^15\)-\(^17\) However, in the past decade, radiation injury to the cochlea has been increasingly recognized as a possible cause of hearing loss and has been the subject of several studies.\(^17\),\(^18\)\(^-\)\(^20\) Although some of these have reported an association between cochlear dose and hearing loss after SRS, others have not found a relation. Therefore, whether and, if so, what cochlear dose constraints should be used to prevent hearing loss is currently ambiguous. Not surprisingly, there is little agreement in the current recommendations: the Congress of Neurological Surgeons consensus guidelines recommend keeping the dose to cochlea <4 Gy; Timmerman\(^21\) suggested a dose limit of 12 Gy maximum point dose, and the UK consensus guidelines suggest a mean dose of 4 Gy, but the Quantitative Analysis of Normal Tissue Effects in the Clinic review does not specify a dose constraint, instead recommending a prescription dose of 12 to 14 Gy.\(^22\),\(^23\),\(^24\)

This study systematically reviews the literature to identify studies that have assessed the relationship between cochlear dose and hearing outcome following SRS for VS. Our aim is to appraise the studies and critically analyze the methods used to assess the strength and significance of the correlation between cochlear dose and hearing loss. To our knowledge, this is the first systematic review of this subject.

Methods and Materials

A literature search of the MEDLINE (via Ovid), Embase (via Ovid), and Scopus databases was performed. The keywords used to develop the search strategy were “acoustic neuroma,” “schwannoma,” “hearing preservation,” “cochlea,” and “stereotactic radiosurgery.” A search strategy was initially developed for Ovid MEDLINE (Appendix E1) and then translated for Ovid Embase and Scopus databases. The Cochrane library was also searched for published reviews that may contain citations relevant to this review. The searches were filtered for articles in English and published after 2000. The study protocol was registered in PROSPERO (CRD42020180960). In view of the publicly available literature under review, research ethics approval was deemed unnecessary.

Publications were included if the study population comprised adults with sporadic VS with serviceable hearing (Gardner-Robertson Class (GRC) I and II or American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS) class A and B), used contemporary radiosurgery doses (11-14 Gy), reported dose to the cochlea, and analyzed its relationship with hearing outcomes. Studies were excluded if the mean or median follow-up after radiosurgery was <24 months, if they were published only in abstract form, or if they included a substantial number of patients with neurofibromatosis 2 or prior radiation therapy treatment.

Two reviewers independently examined the results of the searches. Bibliography search and citation tracking of relevant articles were used to identify other articles. Recent systematic reviews on hearing preservation after radiosurgery treatment were also examined for relevant citations. A predetermined data extraction form guided data extraction.

The quality appraisal was performed using the Newcastle-Ottawa Scale, which assesses observational studies in 3 categories (selection, comparability, and outcome) to a maximum of 9 stars.\(^25\) We used the following criteria (Appendix E2) for awarding stars for the comparability and outcome measures: 1 star if the study controlled for age, marginal dose, and pretreatment hearing status in the design or analysis and 2 stars if tumor volume and fundus distance or fundus involvement were also controlled; 1 star for the length of follow-up only if the follow-up of hearing outcome was >36 months (mean or median).

Results

The database search yielded 2432 articles, and 6 additional articles were identified through bibliography search and citation tracking. The PRISMA (Preferred
Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram is shown in Fig. 1. Twenty-two articles were judged to be relevant and included in this review: 1 retrospective case-control study, and 21 retrospective cohort studies. Although 3 were stated to be prospective\textsuperscript{18,19,26} we instead categorized them as retrospective studies using prospective databases because it was not evident that patients were enrolled in prospective protocols specifically investigating the subject under review. The study characteristics are provided in Table 1. Two studies used linear accelerator SRS; all others used Gamma Knife SRS. Only patients with serviceable hearing (GRC I and II or AAO-HNS class A and B) were included in 8 studies (Table 1). In 1 study, the population was exclusively GRC I; other studies included a mixed population of patients with serviceable and non-serviceable hearing. Two studies included patients treated with SRS or fractionated stereotactic radiation therapy; only the analysis pertaining to the SRS subgroup was extracted from these studies.\textsuperscript{27,28} The cohort in the studies by Regis et al\textsuperscript{29} and Tamura et al\textsuperscript{30} were drawn from the same patient population treated in their institution but varied in the inclusion criteria (GRC I and II vs GRC I only).
| Study                | Year  | Study type                | Patients, n | Pretreatment hearing | Dose            | Machine | Follow-up (mo) | Hearing preservation, % |
|---------------------|-------|---------------------------|-------------|----------------------|-----------------|----------|----------------|------------------------|
| Ottaviani et al     | 2002  | Retrospective             | 26          | Any                  | 12-14 Gy        | GK       | 24 median     | -                      |
| Paek et al          | 2005  | Retrospective             | 25          | GRC I and II         | 11-14 Gy        | GK       | 49 median     | 46 (5 y, actuarial)    |
| Massager et al      | 2007  | Retrospective             | 82          | GRC I-IV             | 12 Gy           | GK       | 24 median     | 56 (4 y, actuarial)    |
| Lasak et al         | 2008  | Retrospective             | 33          | Any                  | 12 or 13 Gy     | GK       | 24 median     | -                      |
| Régis et al         | 2008  | Retrospective             | 184         | GRC I and II         | <13 Gy          | GK       | 84 mean       | 60 (3 y)               |
| Tamura et al        | 2009  | Retrospective             | 74          | GRC I                | 9-13 Gy         | GK       | 48 median     | 78.4 (3 y)             |
| Wackym et al        | 2008  | Retrospective             | 59          | Any                  | 11.7-14 Gy      | GK       | 65.5 median   | -                      |
| Yomo et al          | 2012  | Retrospective             | 154         | Any                  | 9-14 Gy         | GK       | 52 mean       | 58.1                   |
| Kim et al           | 2013  | Retrospective             | 60          | GRC I and II         | 11.5-13 Gy      | GK       | 61.5 mean     | 55 (5 y, actuarial)    |
| Baschnagel et al    | 2013  | Retrospective             | 40          | GRC I and II         | 12.5 or 13 Gy   | GK       | 34.5 median   | 74 (3 y, actuarial)    |
| Carlson et al       | 2013  | Retrospective             | 44          | AAO-HNS A and B      | 12-13 Gy        | GK       | 111.6 median  | 23 (10 y, actuarial)   |
| Jacob et al         | 2014  | Retrospective             | 59          | AAO-HNS A and B      | 12 or 13 Gy     | GK       | 25.2 mean     | 57 (3 y, actuarial)    |
| Horiba et al        | 2016  | Retrospective             | 49          | Any                  | 11-12 Gy        | GK       | 56 median     | 57                     |
| Iorio-Morin et al   | 2016  | Retrospective             | 41          | Any                  | 11-13 Gy        | GK       | 47 median     | 49 (5 y, actuarial)    |
| Lin et al           | 2017  | Retrospective             | 100         | AAO-HNS A and B      | 12 or 13 Gy     | GK       | 78 median     | 63 (5 y)               |
| Pan et al           | 2017  | Retrospective             | 64          | Any                  | 12 Gy           | GK       | 77.9 mean     | 81.2                   |
| Schumacher et al    | 2017  | Retrospective             | 18          | GRC I-IV             | 11 Gy           | GK       | 42 median     | 55                     |
| Park et al          | 2018  | Retrospective             | 56          | Any                  | 10-13 Gy        | GK       | 24.4 mean     | -                      |
| Chung et al         | 2018  | Retrospective, case-control | 14    | GRC I-IV             | 12 Gy           | LINAC    | 38.3 mean     | 64 (5 yr, actuarial)   |
| Prabhraraj et al    | 2019  | Retrospective             | 87          | GRC I and II         | 11.5-14 Gy      | GK       | 30 mean       | 62 (5 y, actuarial)    |
| Patel et al         | 2019  | Retrospective             | 43          | Any                  | 12 Gy           | LINAC    | 25 median     | 53                     |
| Bojrab et al        | 2021  | Retrospective             | 106         | Any (PTA ≤90 dB)     | 12.5 or 13 Gy   | GK       | 49.8 mean     | -                      |

Abbreviations: AAO-HNS = American Academy of Otolaryngology—Head and Neck Surgery Class; GK = Gamma Knife; GRC = Gardner-Robertson Class; LINAC = linear accelerator; PTA = pure-tone average.

* Number of patients in the analysis of predictive factors and hearing outcome.
† Crude rate, unless specified.
‡ Seven patients had secondary GK stereotactic radiosurgery.
§ Only Koos grade 4; 19% had prior resection.
¶ Twenty-one percent had prior resection.
The Newcastle-Ottawa Scale results for included studies are provided in Appendix E3. Scores ranged from 4 to 9 stars (median, 5).

### Cochlea contouring and dosimetry

The cochlea contouring methods varied between studies: 3 used only computed tomography (CT) scan, 4 used magnetic resonance imaging (MRI) and CT, and 4 relied only on MRI (Table 2). The method of contouring the cochlea was not stated in the remainder of the studies. Four studies used cochlear dose constraints in treatment planning (Table 2): Lin et al\(^{31}\) and Baschnagel et al\(^{32}\) met their dose constraint (mean, <5 Gy) in the entire study population, Iorio-Morin et al\(^{33}\) in 18 of the 68 patients, and the proportion of study population that met the constraint (maximum, <4 Gy) was not reported by Horiba et al.\(^{34}\) The studies used various cochlear dose parameters assessed (Table 2): maximum, mean, and minimum, volume receiving 100%, 75%, 50%, and 25% of maximum, dose to modiolus and basal turn of the cochlea.

#### Table 2 Cochlear contouring and cochlear dosimetry in the included studies

| Study              | Year | Cochlear dose constraint | Cochlear contouring | Cochlear dose parameter assessed | Cochlear dose\(^{*}\) (Gy) | Maximum | Mean |
|--------------------|------|--------------------------|---------------------|----------------------------------|-----------------------------|---------|------|
| Ottaviani et al\(^{19}\) | 2002 | -                        | ND                  | Maximum                          | -                           | -       | -    |
| Paek et al\(^{26}\) | 2005 | -                        | ND                  | Maximum and minimum              | 8.1                         | -       |      |
| Massager et al\(^{37}\) | 2007 | -                        | CT and MRI          | Mean, maximum and minimum        | 8.52                        | 4.33    |      |
| Lasak et al\(^{38}\) | 2008 | -                        | MRI                 | Mean                             | -                           | 5.2     |      |
| Régis et al\(^{39}\) | 2008 | -                        | ND                  | Cochlear dose                     | -                           | -       |      |
| Tamura et al\(^{30}\) | 2009 | -                        | CT                  | Dose to modiolus, maximum        | -                           | -       |      |
| Wackym et al\(^{18}\) | 2010 | -                        | ND                  | Maximum, volume receiving 100%, 75%, 50%, and 25% of maximum, dose to modiolus and basal turn of the cochlea | -                           | -       |      |
| Yomo et al\(^{19}\) | 2012 | -                        | CT                  | Maximum                          | -                           | -       | -    |
| Kim et al\(^{63}\) | 2013 | -                        | MRI                 | Mean and maximum                 | 8.2                         | 4.2     |      |
| Baschnagel et al\(^{12}\) | 2013 | Mean, <5 Gy              | CT and MRI          | Maximum, minimum, mean, V3, V5, V8, and V10 | 6.9 (median) | 2.7 (median) |      |
| Carlson et al\(^{13}\) | 2013 | -                        | ND                  | Point modiolus                   | -                           | 5 (modiolus dose) |      |
| Jacob et al\(^{41}\) | 2014 | -                        | CT                  | Mean, maximum, point modiolus    | 11.8                        | 4.9     |      |
| Horiba et al\(^{34}\) | 2016 | Maximum, <4 Gy           | ND                  | Cochlear dose                     | -                           | -       | -    |
| Iorio-Morin et al\(^{13}\) | 2016 | Mean, <4 Gy              | MRI                 | Mean and maximum                 | 6.8 (median) | 4.3 (median) |      |
| Lin et al\(^{31}\) | 2017 | Mean, <5 Gy              | ND                  | Mean, maximum, and minimum       | 5.9                         | 2.8     |      |
| Pan et al\(^{35}\) | 2017 | -                        | MRI                 | Cochlear dose                     | -                           | 3.3     |      |
| Schumacher et al\(^{40}\) | 2017 | -                        | ND                  | Mean and maximum                 | 12 (median) | 6 (median)   |      |
| Park et al\(^{54}\) | 2018 | -                        | ND                  | Mean                             | 8.9                         | 4.6     |      |
| Chung et al\(^{27}\) | 2018 | -                        | CT and MRI          | Mean, maximum, and minimum       | 10.8                        | 8.3     |      |
| Prabhuraj et al\(^{36}\) | 2019 | -                        | ND                  | Mean                             | 5.9                         | 3.74    |      |
| Patel et al\(^{28}\) | 2019 | -                        | CT and MRI          | Mean, maximum, and minimum       | 11.6                        | 8.2     |      |
| Bojrab et al\(^{48}\) | 2021 | -                        | ND                  | Mean and maximum                 | 5.9 (median) | 2.4 (median) |      |

**Abbreviations:** CT = computed tomography; MRI = magnetic resonance imaging; ND = not described.

* Average, unless otherwise specified.
parameters to assess the relationship with the hearing outcomes (Table 2). Three studies did not specify the cochlear dose parameter but instead referred to it simply as “cochlear dose.” Only a point dose at the modiolus was calculated in one study. Although most studies stated that volumetric cochlear dosimetry was performed, whether the maximum cochlear dose corresponded to a point or volume maximum was not always stated.

**Hearing outcomes**

Studies differed in terms of the number and nature of hearing outcomes used, how the hearing loss or deterioration was defined, and the ways the outcome variable was handled (continuous vs dichotomous) (Table 3). The different hearing outcomes and definitions used were as follows:

- Loss of serviceable hearing (GRC III and IV or AAO-HNS class C and D)—dichotomous variable, mostly used in studies that included or analyzed only patients with serviceable hearing
- Increase or loss of baseline GRC or AAO-HNS class—dichotomous variable, used in studies including patients with GRC I only or GRC I to IV
- Change or rate of change in pure-tone average (PTA; difference between pre- and post-SRS PTA) after SRS, without defining a PTA threshold for clinically significant hearing loss or deterioration—continuous variable, used mostly in studies including patients with any hearing level
- Hearing deterioration, defined as the difference between pre- and post-SRS PTA ≥15 dB or 20 dB—dichotomous variable
- Time to non-serviceable hearing—continuous variable.

**Follow-up and timing of hearing outcome assessment**

Although we included only studies with median or mean follow-up of at least 24 months, in some studies, the hearing outcomes were assessed within a much shorter duration after treatment despite having a longer follow-up period (Table 1). Ottaviani et al.19 and Wackym et al.18 assessed PTA change at 24 months and 12 months, respectively. Patel et al.28 assessed the loss of baseline GRC and serviceable hearing at 12 months and last follow-up, and Prabhuraj et al.30 evaluated serviceable hearing preservation at 24 months. The median or mean follow-up was >36 months in 8 studies and >60 months in 6 studies.

**Relationship between cochlear dose and hearing preservation**

Eleven studies reported that the cochlear dose predicted hearing outcome (Table 3). Only a narrative synthesis of the results was possible due to considerable variation in the hearing outcome and the correlating cochlear dose parameter in the studies. Among these 11 studies, not all investigated whether the cochlear dose was an independent predictor of hearing outcome. Wackym et al.,18 Ottaviani et al.,19 Massager et al.,37 and Lasak et al.38 did not include any other predictive factor apart from cochlear dose in their analysis. Other studies assessed various predictive factors but with remarkable variation in their choice of factors (Table 3). Six studies were able to show a correlation between cochlear dose and hearing outcome only in the univariate analysis and not in the multivariate analysis.

In terms of the cochlear dose parameter correlation with hearing outcome, mean dose significantly correlated with hearing preservation in 3 studies,31,37,38 maximum dose in 4,18,27,30,34 mean and maximum dose in 1,40 and minimum dose was found to be the best predictor of hearing preservation in 2 studies.27,28

All 4 studies that used the change in PTA as a continuous outcome variable showed that cochlear dose correlated with hearing outcome (Table 3). However, among these, the study by Lasak et al.38 showed a correlation only between mean cochlear dose and posttreatment speech discrimination score (SDS) but not with PTA. Ottaviani et al.19 showed correlation only between cochlear dose and high-tone audiometry, and Wackym et al.18 assessed change in PTA only during the first 12 months after SRS. All but 1 study that used loss of baseline hearing class as the hearing outcome showed a significant relationship between cochlear dose and hearing outcome (Table 3). On the other hand, only 4 out of 12 studies using loss of functional or serviceable hearing as the outcome revealed a significant relationship (Table 3).

**Cochlear dose threshold for hearing preservation**

Eleven studies provided a cochlear dose threshold or cutoff for better preservation of hearing (Table 3, Fig. 2). Because the cochlear dose threshold for better function or serviceable hearing preservation can be obtained only if functional or serviceable hearing preservation was the outcome, this information was obtainable from only 4 studies. Patel et al.28 showed that hearing preservation was 94% if a cochlear minimum dose cutoff of 5 Gy was met and 13% if not met. Lin et al.31 suggested that a mean cochlear dose <4 Gy predicted better hearing preservation. Schumacher et al.40 showed serviceable hearing...
Table 3  Cochlear dose correlation with hearing outcomes in the included studies

| Study                  | Year | Hearing outcome                                      | Predictive factors analyzed | Cochlear dose predicted hearing outcome (dose parameter) | Cochlea dose threshold                                                                 |
|------------------------|------|------------------------------------------------------|----------------------------|--------------------------------------------------------|----------------------------------------------------------------------------------------|
| Chung et al[27]         | 2018 | Stable vs decreased hearing at last follow-up        | Patient, tumor, and dosimetric | -                                                      | Yes (minimum)                                                                          |
|                        |      |                                                      |                            |                                                        | Cochlear minimum dose of >6 Gy was associated with higher risk for hearing deterioration |
| Massager et al[37]     | 2007 | Hearing preservation (same or improved GRC)         | None                       | Yes (mean)                                             | -                                                                                      |
|                        |      |                                                      |                            |                                                        | Median mean dose to cochlear volume: 3.7 Gy (hearing preserved) vs 5.33 Gy (hearing deteriorated) |
| Lin et al[31]          | 2017 | Hearing preservation (AAO-HNS A or B)               | Patient, tumor, and dosimetric | Yes (mean); only predictor                            | -                                                                                      |
|                        |      |                                                      |                            |                                                        | Mean dose of <4 Gy favorable predictor of hearing outcome                               |
| Régis et al[29]        | 2008 | Loss of functional hearing (GRC I and II)           | Patient, tumor, and dosimetric | -                                                      | Yes                                                                                   |
|                        |      |                                                      |                            |                                                        | -                                                                                      |
| Prabhuraj et al[36]    | 2019 | Hearing preservation (GRC I and II) at 24 mo        | Patient and tumor          | Yes (mean)                                             | No                                                                                     |
| Pan et al[35]          | 2017 | Preservation of serviceable hearing (<50 dB and ≥50% SD) | Tumor and dosimetric      | Yes                                                    | No                                                                                     |
| Iorio-Morin et al[33]  | 2016 | Preservation of serviceable hearing (GRC I and II)   | Tumor and treatment-related | No                                                     | -                                                                                      |
| Horiba et al[34]       | 2016 | Preservation of serviceable hearing (GRC I and II)   | Patient, tumor, and dosimetric | No                                                     | -                                                                                      |
| Tamura et al[30]       | 2009 | Preservation of GRC I and functional hearing preservation (GRC I and II) | Patient, tumor, and dosimetric | -                                                      | Yes (maximum), for GRC I preservation                                                  |
|                        |      |                                                      |                            |                                                        | 90.9% functional hearing preservation; for maximum cochlear dose of <4 Gy               |
| Baschnagel et al[32]   | 2013 | Serviceable hearing (GRC I and II) and maintain GRC | Patient, tumor, and dosimetric | Yes (mean and % volume ≥3 Gy)                        | No                                                                                     |
|                        |      |                                                      |                            |                                                        | Mean cochlear dose of <3 Gy associated with better serviceable hearing preservation (trend toward statistical significance); 2-y hearing preservation: 91% (mean dose, <3 Gy) vs 59% (mean dose, ≥3 Gy) |

(continued on next page)
| Study          | Year | Hearing outcome                                | Predictive factors analyzed | Cochlear dose predicted hearing outcome (dose parameter)                                                                 |
|---------------|------|-----------------------------------------------|----------------------------|--------------------------------------------------------------------------------------------------------------------------|
| Patel et al²⁸ | 2019 | Loss of baseline GRC and loss of serviceable hearing at 1 y and last follow-up | Patient and tumor¹          | Univariate analysis: Yes (minimum, mean, and maximum); only predictors<br>Median and minimum correlated with both outcomes, maximum only with loss of GRC. Minimum dose was the most robust predictor; hearing preservation: 94% (minimum, <5 Gy) vs 13% (minimum, ≥5 Gy) |
| Schumacher et al⁴⁰ | 2017 | Loss of baseline GRC and loss of serviceable hearing | Patient, tumor, and dosimetric | Multivariate analysis: Yes (mean and maximum) Mean dose correlated with both outcomes, maximum only with loss of GRC; serviceable hearing preservation: 100% (mean, <6 Gy) vs 13% (mean, ≥6 Gy). GRC preservation: 89% (maximum dose, <12 Gy) vs 20% (maximum dose, ≥12 Gy) |
| Lasak et al³⁸ | 2008 | Change in PTA and SDS                         | None                        | Univariate analysis: Yes (mean)                                                                 Only minimum SDS after SRS correlated with mean cochlear dose; at 12 mo, change in PTA was significantly worse for mean cochlear dose ≥4.75 Gy |
| Wackym et al¹⁸ | 2010 | Change in PTA³, PTA⁴, PTA-HF,¹ and speech recognition during first 12 mo | None                        | Univariate analysis: Yes (maximum)                                                                 Cochlear dose >4 Gy correlated with change in PTA³ |
| Yomo et al³⁹  | 2012 | Annual rate of PTA decrease (dB/y)            | Patient and tumor            | Univariate analysis: Yes (maximum) Maximum cochlear dose (≤4 Gy) was a statistically significant predictive factor. Hearing decrease: 3.14 dB/y (maximum dose, ≤4 Gy) vs 4.43 dB/y (maximum dose, >4 Gy) |
| Ottaviani et al¹⁹ | 2002 | 2-y decrease in LTA, PTA, and HTA            | None                        | Univariate analysis: Yes (maximum; correlated only with HTA)                                                            |
Table 3 (Continued)

| Study*          | Year | Hearing outcome | Predictive factors analyzed | Cochlear dose predicted hearing outcome (dose parameter) | Univariate analysis | Multivariate analysis | Cochlea dose threshold |
|-----------------|------|-----------------|-----------------------------|--------------------------------------------------------|---------------------|----------------------|------------------------|
| **Hearing outcome: change in PTA (dichotomous outcome)** |      |                 |                             |                                                        |                     |                      |                        |
| Park et al54    | 2018 | PTA increase ≥15 dB | Patient, tumor, and dosimetric | Yes No -                                               |                     |                      |                        |
| Paek et al26    | 2005 | PTA increase ≥20 dB | Dose to cochlear nerve and cochlear nucleus | No - -                                               |                     |                      |                        |
| **Hearing outcome: time to hearing loss (continuous outcome)** |      |                 |                             |                                                        |                     |                      |                        |
| Carlson et al13 | 2013 | Time to nonserviceable hearing | Patient, tumor, and dosimetric | No - -                                               |                     |                      |                        |
| Jacob et al41   | 2014 | Time to nonserviceable hearing | Patient, tumor, and dosimetric | Yes (mean) No - -                                      |                     |                      | 3-y serviceable hearing preservation: 76% (mean dose, <5 Gy) vs 37% (mean dose, ≥5 Gy) |
| **Hearing outcome: loss of serviceable hearing and change in PTA (dichotomous outcomes)** |      |                 |                             |                                                        |                     |                      |                        |
| Kim et al53     | 2013 | Preservation of serviceable hearing (GRC I and II) and hearing deterioration (PTA increase ≥20) | Patient, tumor, and dosimetric | Yes (mean) No - -                                      |                     |                      |                        |
| Bojrab et al48  | 2021 | Maintenance of AAO-HNS A or B and hearing preservation (PTA increase ≤20 dB) | Tumor and dosimetric factors | No - -                                               |                     |                      |                        |

Abbreviations: AAO-HNS = American Academy of Otolaryngology—Head and Neck Surgery Class; FSRT = fractionated stereotactic radiation therapy; GRC = Gardner-Robertson Class; HTA = low-tone average; LTA = high-tone average; PTA = pure-tone average; PTA-HF, pure-tone average high frequency; SDS = speech discrimination score; SRS = stereotactic radiosurgery.

* Studies are ordered based on method of hearing outcome assessment.
† SRS and FSRT groups combined to analyze tumor and patient-related factors.
‡ PTA3 to 500, 1000, and 2000Hz.
§ PTA4 to 500, 1000, and 2000 Hz.
|| PTA-HF to 4000, 6000, and 8000 Hz.
preservation was 100% for a mean cochlear dose <6 Gy compared with 13% for >6 Gy. Tamura et al\textsuperscript{30} also showed that functional hearing preservation was 90% when the maximum dose was <4 Gy.

Two studies that did not show a significant correlation in the multivariate analysis also described hearing preservation in relation to cochlear dose. Baschnagel et al\textsuperscript{32} showed that no patient with a mean cochlear dose <2 Gy lost serviceable hearing, and when the mean dose was <3 Gy, the chance of maintaining serviceable hearing at 2 years was 91%. However, mean cochlear dose showed only a trend toward statistical significance as an independent predictor. In the study by Jacob et al\textsuperscript{41}, which used the time to nonserviceable hearing loss as the outcome, the 3-year serviceable hearing preservation was 76% for a mean dose < 5 Gy, whereas it was 37% for mean dose ≥5 Gy.

In the studies using change in PTA as the hearing outcome, Wackym et al\textsuperscript{18} showed that a maximum cochlear dose >4 Gy correlated with change in PTA during first 12 months after SRS. Similarly, Yomo et al\textsuperscript{39} showed that a cochlear dose ≤4 Gy was associated with a lower rate of change in PTA than >4 Gy (3.14 dB/y vs 4.43 dB/y). Mean cochlear dose of ≥4.75 Gy was associated with significantly worse PTA at 12 months, in Lasak et al’s\textsuperscript{38} study, but the correlation was not significant in stepwise regression analysis.

Among only studies that used any change in baseline hearing class as the hearing outcome, Chung et al\textsuperscript{27} reported that a minimum cochlear dose of >6 Gy was associated with a higher risk for hearing deterioration, and Massager et al\textsuperscript{37} showed the median mean dose to cochlea was 3.7 Gy for the group that maintained baseline GRC and 5.33 Gy for those that lost GRC.

**Discussion**

This appears to be the first systematic literature review on cochlear dose in relation to hearing preservation after SRS for VS. It has revealed that all of the existing data are retrospective (albeit some obtained from prospective databases), with considerable heterogeneity in definitions and reporting of outcomes, precluding formal meta-analysis and definitive recommendations. We highlight and discuss some of the important study variables that affected interpretation.

**Cochlear contouring and dosimetry**

The cochlear contouring was not consistent between studies, differing by the imaging modality used and whether the whole cochlea was contoured. Kulkarni et al\textsuperscript{12} found that cochlear volume based on MRI (T2-weighted) was larger than CT. However, despite the poor correlation in cochlear volume between CT and MRI contouring, Faramand et al\textsuperscript{43} did not find any significant
dosimetric disagreement, perhaps due to the small volume of the cochlea. Hence, we believe that CT or MRI may be acceptable as long as the whole cochlea is contoured. However, CT bone window may be preferable for contouring due to the superior resolution of the bony anatomy of the cochlea and because MRI can be affected by distortion, particularly when dealing with small structures such as the cochlea.\(^{41,44}\) Using only the modiolus dose is not favored as many structures within the cochlea—namely, stria vascularis and basal turn of the cochlea—are possible targets of radiation damage.\(^{18,45}\) Therefore, cochlear dosimetry should be based on the whole volume to best represent the dose received by the cochlea.\(^{11}\)

The discrepancy in the cochlear dose parameters reported to correlate with hearing outcome and the variation in dose threshold for better hearing preservation (a mean dose of 3-6 Gy, a maximum dose of 4-12 Gy, and a minimum dose of 5-6 Gy) also impaired comparison between studies. In principle, comparison between different dose parameters is possible as there seems to be an inherent relationship between various cochlear dose parameters. Ma et al\(^{16}\) investigated the relationship between maximum point dose to cochlea and cochlear mean dose; modiolus dose; and dose to 0.01, 0.02, and 0.03 mL, showing a strong correlation between these parameters: the cochlear mean dose and modiolus dose were one-half of the maximum point dose and similar to the dose to 0.03 mL of the cochlea. However, in practice, we could not undertake any such comparisons between studies because they did not mention if the maximum dose corresponded to point or volume maximum.

### Hearing outcome assessment

**Functional or serviceable hearing loss as outcome**

Using functional or serviceable hearing loss as the outcome measure has its advantages. First, it is a standardized and clinically useful endpoint that allows easy comparison between studies. Second, by correlating cochlear dose with this endpoint, it would be possible to determine a cochlear dose threshold that could be employed in treatment planning for better preservation of serviceable hearing. However, it has disadvantages that hinder the assessment of correlation between cochlear dose and hearing outcome.

The first disadvantage is due to the use of a cutoff (50 dB and 50% SDS) to define serviceable hearing loss. The time point when serviceable hearing will be lost depends on pretreatment PTA and the rate of hearing loss. The average PTA loss after SRS has been reported to be around 4 to 7 dB/y in the first 24 to 36 months after treatment and at a slower rate thereafter.\(^{39,42}\) Hence, a lower pretreatment PTA will mean that it will take longer to reach the threshold of serviceable hearing loss; in other words, patients with GRC I may have a longer duration of serviceable hearing than GRC II.\(^{48}\) This time lag created by using an arbitrary cutoff can deceptively associate pretreatment PTA or GRC with the hearing outcome, especially if the follow-up period is not long enough. Linge et al\(^{49}\) demonstrated this problem in their study, which analyzed the hearing outcome in 3 different ways: functional hearing loss, loss of baseline GRC, and PTA increase per month. The pretreatment PTA and V90 of the cochlea were associated with hearing outcomes if the endpoint was functional hearing loss (GRC I and II) or loss of baseline GRC. However, the pretreatment PTA was not associated with hearing outcome when rate of change of PTA was used as the endpoint, but V90 of the cochlea remained significant. Similarly, if the time to serviceable hearing loss is used as the hearing outcome measure, then one would anticipate pretreatment PTA will be a strong prognostic factor. This is evident in the study by Jacob et al,\(^{11}\) which used the time to serviceable hearing loss as the outcome. This study showed that the cochlear dose was a significant predictor of hearing outcome but lost significance when multivariate analysis adjusted for pretreatment PTA.

The second disadvantage emerges due to the grouping of PTA data into classes (GRC I and II or AAO-HNS class A and B) to define serviceable hearing, frequently employed in studies that use serviceable hearing loss as the outcome. The grouping of PTA data into hearing classes results in loss of granularity of the data and is less sensitive to changes in PTA, compared with using difference in PTA as a continuous outcome.\(^{49}\)

The previously discussed factors suggest that pretreatment PTA or hearing class (GRC I) may appear to be stronger predictive factors than the cochlear dose if functional hearing preservation or the time to serviceable hearing loss is used as the endpoint. Perhaps this explains why a much lower proportion of studies that used functional or serviceable hearing loss, and neither of the 2 studies that used the time to serviceable hearing loss as the outcome was able to show that cochlear dose was an independent predictor of hearing loss compared with studies that used loss of hearing class or only change in PTA as endpoints.

**Loss of baseline GRC as hearing outcome**

Five of the 6 studies using loss of baseline GRC as the hearing outcome showed that cochlear dose was a predictive factor, notwithstanding the differences in their patient populations. Except for Tamura et al,\(^{30}\) who included only patients in GRC I, others had patients with GRC I to IV. It must be noted that Massager et al\(^{37}\) did not assess other predictive factors of hearing loss; hence, it is not clear whether cochlear dose was an independent prognostic factor. Allowing for the heterogeneity between these studies, why a substantially higher proportion using loss of baseline GRC showed correlation, compared with studies using serviceable hearing loss as the outcome, is unclear.
It may be that the sensitivity of the outcome to change in hearing increases when the endpoint is defined as an improvement in hearing class by 1 level only.

**Change in PTA as outcome**

Using the change in PTA as the hearing outcome may appear to be a better strategy due to the previously discussed issues with using serviceable hearing loss as the outcome. Moreover, by using change in PTA, studies can use a larger patient population (not limited to GRC I and II or AAO-HNS class A and B) and, as a result, may have a better chance of showing significant correlation.\(^\text{48}\)

Change or rate of change of PTA is also a continuous variable. Although debatable, the hearing outcome as a continuous rather than dichotomous variable may be more suitable for the statistical analysis of the correlation between hearing outcome and cochlear dose. Brown et al.'s\(^\text{50}\) study is a case in point. They analyzed the correlation between cochlear dose and hearing outcome as a continuous variable (difference in PTA) and dichotomous variable (change in PTA, <20 dB or ≥20 dB) and showed that cochlear dose (volume receiving >5.3 Gy) correlated only with the difference in PTA as a continuous outcome.

However, using change in PTA, too, has its disadvantages. First, as a hearing outcome, difference in PTA is not as clinically applicable as preservation of serviceable hearing and will not be well suited to assess the cochlear dose threshold for hearing preservation. Moreover, what PTA difference (10, 15, or 20 dB) represents a clinically significant loss is unclear. Second, the time-dependent nonlinearity of PTA can pose problems. As previously mentioned, the rate of change of PTA is faster in the first 24 to 36 months after treatment, followed by a longer period of many years with a slower rate of change.\(^\text{31,39,47}\) Not only can this cause problems with statistical analysis, but studies with different duration of follow-up can end up showing different results: studies with short follow-up are more likely to show significant correlation. Of the 4 studies that showed a correlation between cochlear dose and difference in PTA, 3 studies assessed PTA difference only up to 24 months; whether the correlation would remain true on longer follow-up is uncertain. However, one could argue that hearing loss due to cochlear irradiation should manifest within the first few years after SRS when the acute decline in PTA is demonstrated.\(^\text{51}\)

**Study limitations**

It is generally agreed that hearing loss after SRS for VS is a complex process, and there are possibly multiple factors that determine hearing preservation. However, by focusing only on the cochlear dose, we have not considered other factors that may also need to be considered.

We identified studies by scrutinizing their title and abstract for the mention of cochlear dose. Hence, there is potential for selection bias by not including studies that did not mention cochlear dose owing to the lack of correlation. By excluding studies that used doses higher than 14 Gy, we may have overlooked useful information that could have been obtained from such studies possibly demonstrating cochlear dose to be a predictive factor. It should also be noted that the tool we used for appraising study quality has been subject to criticism in relation to scoring consistency.\(^\text{52}\)

**Conclusion**

Despite accumulating evidence, it is still ambiguous if cochlear dose is an independent predictor of hearing preservation after SRS for VS. Without consistency between studies in relation to cochlear dosimetry and hearing outcomes, the cochlear dose tolerance is uncertain. However, based on currently available data, a practical approach will be to aim for a mean cochlear dose < 4 to 6 Gy without compromising tumor dose. We recommend future studies to report all cochlear dose parameters and multiple endpoints, such as the change in PTA, functional hearing preservation, and the preservation of baseline hearing class.

**Supplementary materials**

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2022.101059.

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