Hearing preservation in vestibular schwannoma stereotactic radiosurgery: what really matters?

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Stereotactic radiosurgery (SRS) for vestibular schwannomas has evolved and improved over time. Although early short-term follow-up reports suggest that fractionation yields hearing preservation rates equivalent to modern single-dose SRS techniques, significant questions remain regarding long-term tumor control after the use of fractionation in a late responding tumor with a low proliferative index and α/β ratio. With single-dose SRS, critical hearing preservation variables include: 1) strict attention to prescription dose 3D conformity so that the ventral cochlear nucleus (VCN) receives ≤ 9 Gy; 2) careful delineation of the 3D tumor margin to exclude the cochlear nerve when visualizable with contrast-enhanced T2-weighted MR volumetric imaging techniques and exclusion the dura mater of the anterior border of the internal auditory canal; 3) a tumor margin dose prescription ≤ 12 Gy; 4) optimization of the tumor treatment gradient index without sacrificing coverage and conformity; and 5) strict attention to prescription dose 3D conformity so that the modiolus and the basal turn of the cochlea receive the lowest possible dose (ideally < 4–5.33 Gy). Testable correlates for the relative importance of the VCN versus cochlear dose given the tonotopic organization of each structure suggests that VCN toxicity should lead to preferential loss of low hearing frequencies, while cochlear toxicity should lead to preferential loss of high hearing frequencies. The potential after SRS for hearing toxicity from altered endolymph and/or perilymph fluid dynamics either via impaired fluid production and/or absorption has yet to be explored. Serous otitis media, ossicular or temporal bone osteonecrosis, and chondromalacia are not likely to be relevant factors or considerations for hearing preservation after SRS.

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**Key Words** • Gamma Knife radiosurgery • hearing preservation • stereotactic radiosurgery • temporal bone • vestibular schwannoma

**Abbreviations used in this paper:** DCN = dorsal cochlear nucleus; GKS = Gamma Knife surgery; IAC = internal auditory canal; SRS = stereotactic radiosurgery; VCN = ventral cochlear nucleus; VS = vestibular schwannoma.
it is very important that we do not lose our therapeutic priorities, our professional compass so to speak, when it comes to applying SRS in patients with VSs. Our primary goal as surgeons is always first to provide permanent control of the tumor, whether we remove it or treat with SRS. Elimination of all complications is not the primary goal. The primary goal is permanent tumor control with the lowest possible cranial nerve complication rate. If we preserve cranial nerve function in the short term only to lose tumor control 10–15 years later, we have done our patients a disservice. They will never be younger or healthier, and the tumor will never be smaller and safer to treat than in the present.

Schwannomas are late responding tissues with low proliferative indices and a low α/β ratio for application of the linear quadratic formula. From a radiobiological standpoint, these circumstances favor superior tumor control response from a single, highest-possible radiation dose (such as single-dose SRS), compared with multiple smaller doses. An analogous example is another benign slowly growing tumor, the meningioma. Empirical experience has confirmed that at least 10 years of neuroimaging follow-up, or even 20 years of clinical follow-up (in the absence of imaging) is necessary to rule out recurrence or progression. Treating benign meningiomas with fractionated radiotherapy only yields a 76–81% tumor control rate over 8–15 years, compared with a 93% 10-year, imaging-confirmed, tumor control rate with single-dose SRS. Although the authors of a comparative study using 25 2-Gy fractions and those of various other case series using noncomparative 2–5 fraction SRS have suggested that fractionation techniques for VS may yield equivalent, or even improved, short-term hearing preservation rates compared with modern single-dose SRS techniques, no comparative study has been performed for 2–5 dose SRS versus single-dose SRS, and significant questions and concerns remain that with fractionation, hearing preservation may be achieved at the expense of reduced long-term schwannoma tumor control rates.

**Brainstem Factors**

Tumor-treatment volume conformality on every tumor surface in all 3 dimensions is critically important for optimal GKS. For hearing preservation the key structures to spare within the brainstem are the VCN and DCN. These 2 cranial nerve nuclei are located at the level of the lateral recess of the fourth ventricle at the pontomedullar junction demonstrating the root entry zone of the VII and VII cranial nerves as well as the VCN and the DCN. The cochlear nuclei are tonotopically organized with low frequencies (L) represented ventral and laterally, mid frequencies represented in the center of each nucleus (M), and high frequencies (H) represented medially and dorsally. The cochlear nerve splits the VCN and the DCN and the medial low frequency portion (*) is located at a slightly more caudal level. B: with the location of a vestibular schwannoma indicated within the cerebellopontine angle (Tumor), it becomes clear that the low frequency representations of the cochlear nuclei are closest to the tumor margin and differentially susceptible to radiosurgery toxicity.

**TABLE 1**

<p>| Variables to consider when planning and prescribing SRS dose for VS |
|---|---|---|---|</p>
<table>
<thead>
<tr>
<th>Tumor</th>
<th>Nerve</th>
<th>Brainstem</th>
<th>Temporal Bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>margin dose</td>
<td>exclusion from tumor volume</td>
<td>VCN</td>
<td>cochlea</td>
</tr>
<tr>
<td>conformity</td>
<td>tumor margin dose</td>
<td>modiolus spiral ganglion</td>
<td>other temporal bone structures</td>
</tr>
<tr>
<td>gradient index</td>
<td>gradient index</td>
<td>DCN</td>
<td>basal turn</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>inner ear (endolymph/perilymph)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>middle ear (mucosa, ossicles &amp; Eustachian tube)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>apical turn</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>external ear</td>
</tr>
</tbody>
</table>

**Fig. 1.** A: Nissl stained cross section 14x of the brainstem at the level of the lateral recess of the fourth ventricle at the pons-medullar junction demonstrating the root entry zone of the VII and VII cranial nerves as well as the VCN and the DCN. The cochlear nuclei are tonotopically organized with low frequencies (L) represented ventral and laterally, mid frequencies represented in the center of each nucleus (M), and high frequencies (H) represented medially and dorsally. The cochlear nerve splits the VCN and the DCN and the medial low frequency portion of the DCN (*) is located at a slightly more caudal level. B: with the location of a vestibular schwannoma indicated within the cerebellopontine angle (Tumor), it becomes clear that the low frequency representations of the cochlear nuclei are closest to the tumor margin and differentially susceptible to radiosurgery toxicity.
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auditory implantation must be inserted and stabilized. The cochlear nerve ends up splitting the VCN and DCN, with the DCN extending slightly more caudal in the brainstem than the VCN. The VCN is closest to the potential tumor–brainstem interface, and thus most susceptible to unexpected or higher dose exposure. Both nuclei are tonotopically organized by frequency with lower hearing frequencies represented more ventrally and laterally; closest to the potential tumor–brainstem interface. A testable corollary to this observation is that hearing loss after SRS due to VCN toxicity should manifest as preferential loss of lower frequency tones.

### TABLE 2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Preserved (PTA Loss &lt;20 dB)</th>
<th>Deteriorated (PTA &gt;20 dB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>max (Gy)</td>
<td>6.9 ± 4.5</td>
<td>11.1 ± 3.9</td>
</tr>
<tr>
<td>min (Gy)</td>
<td>3.8 ± 4.2</td>
<td>5.1 ± 2.1</td>
</tr>
<tr>
<td>calculated cochlear nucleus isodose line given 12-Gy mean prescription</td>
<td>10–47.3% isodose line</td>
<td>30–62.25% isodose line</td>
</tr>
<tr>
<td>dose to 49.8% isodose line at tumor margin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adapted from data presented in Paek et al., 2005. PTA = pure tone average.

![Fig. 2. Heavily T2-weighted volumetric, contrast-enhanced target image of a left VS. Inferior level (A) and superior level (B) revealing cranial nerve VIII relative to the tumor volume, and (C) GKS dose plan prescribing 12 Gy to the 50% isodose line, taking these relationships into account.](image-url)
To date, only 1 study of hearing preservation after GKS has implicated cochlear nucleus toxicity as having a statistically significant impact. In 2005 Paek et al.\textsuperscript{32} noted that their patients who lost useful hearing received a mean maximum cochlear nucleus dose of 11.1 ± 3.9 versus 6.9 ± 4.5 Gy for those in whom hearing was preserved (Table 2), and that this result was statistically significant. The break point between the 2 groups would be at 9 Gy, but there are large SD overlaps between the 2 groups. Unfortunately, the methods section of their paper does not describe the location and method for cochlear nucleus sampling, so distinctions between VCN and DCN cannot be made. The authors also did not break down the hearing loss observed by frequency tone to confirm their conclusion that toxicity was localized to the cochlear nucleus. It is also important to note that correlating the mean tumor prescription dose of 12 Gy at an isodose of 49.8% with the range of maximum doses to the cochlear nucleus (Table 2) indicates that in the hearing loss group, the cochlear nucleus within the brainstem was enclosed by an isodose line as high as 30% in some cases. This observation might suggest a potential problem with suboptimal 3D dose planning conformity in this region. To date, the cochlear nucleus toxicity observation of Paek et al. has not been confirmed by any other SRS study, and our own data do not support this association at the present time.

### Dose Prescription

Most radiation complications follow a dose-volume relationship.\textsuperscript{7,13} In cranial nerves, the dose-volume relationship is not determined by the volume of the tumor treated, but the volume of treated nerve. The volume of nerve treated can vary among tumors with the same 3D volume depending on their tumor–nerve surface interface. For long thin structures such as nerves, the volume of nerve exposed is best approximated by the nerve length apposed to the tumor surface. For VSs and somatic cranial nerves V and VII, where doses of 12–20 Gy are applied, the volume of cranial nerve exposed is more predictive of subsequent cranial neuropathy than either tumor margin dose or tumor volume.\textsuperscript{18} However, in the cochlear nerve, a special sensory cranial nerve, this correlation dose not hold, and dose alone appears to be the most important factor.\textsuperscript{19} Using empiric dose data of 12–20 Gy and then extrapolating to lower doses, Flickinger and colleagues\textsuperscript{8} predicted hearing preservation rates of 70–82% with VS margin doses of 10–13 Gy (Table 3). These predictions have been shown to be accurate, if somewhat conservative. In 2007 the University of Pittsburgh group\textsuperscript{4} reported a 74% useful hearing preservation rate after 12–13 Gy GKS (versus 70–72% predicted by earlier 1996 dose-data extrapolation). Importantly, the 10-year neuroimaging confirmed tumor control rate using 12–13 Gy was 98%, confirming that at least with a 12-Gy dose we are not in danger of compromising our therapeutic priorities or losing our professional compass.\textsuperscript{6} Current GKS VS hearing preservation doses are 10–12 Gy.

### Cochlear Nerve Exclusion From Target Volume

A dose > 12 Gy could inadvertently be delivered to the cochlear nerve if the tumor margin were misdrawn on the dose planning software in such a way that the cochlear nerve ended up apparently deeper within the tumor volume. To avoid this it is critically important to try to visualize the cranial nerve–VS interface and separate the cranial nerves from the tumor edge. A major advance in this capability came with observation of Régis et al.,\textsuperscript{33} who noted that applying contrast enhancement during heavily T2-weighted MR volume acquisitions could differentially lighten the tumor signal to the point where cranial nerves VII and VIII could be distinguished on the VS tumor surface. We now routinely apply target imaging sequences along with T1-weighted, spoiled gradient echo volume sequences during VS targeting (Fig. 3). For small VSs (particularly those restricted to the IAC), the complete tumor–cranial nerve interface can often be distinguished and the cranial nerves excluded from the target volume. For larger VSs the cranial nerve–tumor interface is often lost within the IAC, but can still usually be made out in the cerebellopontine angle. For cases in which the cranial nerve–tumor distinction is lost within the IAC, we feel it is important to recognize that IAC enhancement includes not only tumor, but also the dura lining the IAC. In cases in which the patient’s dura has a defined width of enhancement in areas not involved with tumor (such as lining the clivus or the contralateral petrous face), we subtract this defined width from the anterior edge of the IAC enhancement to ensure that we are not erroneously extending the perceived tumor limits beyond the IAC course of the cranial nerves.

### Tumor Parameters

In their patients treated for VS with GKS, Massager et al.\textsuperscript{23} found that preservation of hearing correlated with the 3D volume of tumor in the IAC and with the integral dose delivered to the IAC tumor volume. This finding has not been reproduced by others, and has been specifically examined and found not to correlate in the Marseilles group GKS VS population.\textsuperscript{36} Dose within the substance of a tumor would seem only to make sense in a dose-threshold situation for circumstances in which the cochlear nerve would not lie on the surface of the tumor but might be lodged within the substance of the tumor. As this situation has been described for VSs in the special setting of neurofibromatosis Type 2,\textsuperscript{22,26} dose homogeneity within the tumor and the integral tumor dose might turn out to be important in this special circumstance.
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For unilateral VSs in patients without neurofibromatosis Type 2, the steepness of radiation fall-off at the tumor cranial nerve or other critical structure interface will determine the dose delivered to those structures and is of paramount importance. For GKS, the 4-mm collimator has the best and steepest dose fall-off profile of all available collimators. For this reason we recommend using only the 4-mm collimator in the IAC. In addition, great care must be taken when utilizing sector blocking or hybrid isocenters with the new Perfexion Gamma Knife unit (Elekta AB) because these sector variations can adversely affect the 4-mm radiation fall-off profile and the radiosurgeon must ensure that this fall-off degradation dose does not occur at the tumor–cranial nerve or tumor–critical structure interface. One way of assessing the steepness of the radiation fall-off between different potential dose plans is by utilizing the gradient index defined as 1/2 margin dose volume/margin dose volume (ideal target value 2.5). However, this index indiscriminately measures fall-off around the entire 3D surface of the tumor, when the area of concern may only lie in 1 sector such as the anterior surface of the tumor in the IAC. As a result we prefer to prioritize the linear distance between the dose prescription isodose line and the 50% of

Fig. 3. A: Cadaver histological transverse section through the temporal bone at the level of the modiolus of the cochlea (M) demonstrating the cochlear nerve (CN), the lamina spiralis ossea (LSO), the scala vestibule (SV), the scala tympani (ST) and the ligamentum spirale cochleae (LSC). B: T2-weighted MR image demonstrating the same structures. C: Computed tomography bone window scan at the level of the modiolus indicating the area for point dose sampling after SRS. D: Computed tomography bone window scan at the level of the inferior basal turn of the cochlea indicating the area for point dose sampling after SRS.
dose prescription isodose line as another direct measure of steepness of fall off that can be specific to the critical interface in question. For the anterior surface of the IAC this is often best assessed on serial sagittal plane targeting images.

**Cochlea**

We were the first to take an interest in normal temporal bone structure exposure during SRS for VS, as well as to explore the potential implications for SRS toxicity.\(^{19,20}\) In a study of VS GKS dose plans in an open GK unit involving 15 different team combinations of neurosurgeons and radiation oncologists performed in 1999, we noted that the cochlea had 2 separate areas where it was prone to inadvertently receiving an unexpectedly high dose (Table 4). The inferior basal turn of the cochlea received an unexpectedly high dose 14.8% of the time and the modiolus of the cochlea received an unexpectedly high dose 10.8% of the time (Fig. 3).\(^{20}\) The modiolus contains the spiral ganglion, is easily recognized on CT and MR, and is located at the level of the superior portion of the basal turn and the inferior portion of the apical turn of the cochlea (Fig. 2). Just like the brainstem cochlear nuclei, the cochlea is also tonotopically organized with higher frequencies at the most inferior basal portion and the lowest frequencies at the most apical portion (Fig. 4).\(^{23}\) A testable corollary to this observation is that hearing loss after SRS due to cochlea toxicity should manifest as preferential loss of high-frequency tones.

Given the nature and structure of an open Gamma Knife system, we were not able to link our statistical associations with clinical outcomes. The first to attempt to link cochlear dose with hearing preservation outcomes with VS GKS was made by Paek et al.\(^{32}\) in 2005, who found no statistical correlation. The first to demonstrate that this association existed and was important was Jean Régis and his team\(^{33}\) in Marseilles, France who presented their results in a public forum in 2007. This was followed by the first publication of the importance of the cochlear dose to hearing preservation after SRS for VS by the Brussels Belgium GKS group in late 2007.\(^{27}\) The Marseilles team measured point doses at the modiolus of the cochlea. Unfortunately they did not measure doses at the inferior basal turn of the cochlea which might be even more susceptible.\(^{20}\) They were, however, able to show that patients with modiolus doses < 4 Gy had a significantly higher chance of preserving hearing than those exposed to higher doses. These 2 groups of patients divided into widely divergent Kaplan-Meier life table curves that differed significantly by log-rank test (p = 0.014).\(^{36}\) Massager et al.\(^{27}\) took a different approach. They measured the mean cochlear dose averaged over the whole 3D volume of the cochlea and found that those with preserved hearing had a mean cochlea dose of 3.70 versus 5.33 Gy in those who lost useful hearing. Unfortunately, by including the apical turn of the cochlea, which is least susceptible to high dose\(^{20}\) in the volume average, the significant dose level may be diluted downward as a result. The cochlear threshold dose requires further validation and confirmation, but probably lies somewhere in the range of 4–5.33 Gy.

**Other Temporal Bone Structure Considerations**

Another consideration that may have an impact on hearing function is the dynamics of endolymph and perilymph production, pressure, and absorption. High inner...
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TABLE 5
Calculated single dose thresholds a

<table>
<thead>
<tr>
<th>Dose Threshold (External &amp; Middle Ear)</th>
<th>2 Gy/Fraction</th>
<th>Single Fraction</th>
<th>2 Gy/Fraction</th>
<th>Single Fraction</th>
<th>2 Gy/Fraction</th>
<th>Single Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>chronic otitis</td>
<td>55</td>
<td>15.4</td>
<td>52</td>
<td>15.0</td>
<td>79</td>
<td>18.9</td>
</tr>
<tr>
<td>bone necrosis</td>
<td>65</td>
<td>16.9</td>
<td>65</td>
<td>16.9</td>
<td>90</td>
<td>20.3</td>
</tr>
</tbody>
</table>

* The linear quadratic equation states that: the biologically effective dose = α nd + β nd² (Equation 1). Where n is the number of fractions of dose d (in Gy), and α and β are coefficients of the effect of dose. If equivalent biological endpoints are compared between 2 different dose fractionation schemes, Equation 1 is rearranged to show: n₁d₁² = n₂d₂ (α/β + d₁) / (α/β + d₂) (Equation 2). If a standard d₁ of 2 Gy is chosen, then n₁d₁² may be set equal to the TD50/5 or TD50/5, both of which are defined for conventional fractionation. Thus, because n₁ = 1 for GKS, d₁ will represent the single dose equivalent to the respective toxicity dose. Assuming an α/β ratio of 3.3, no time factor, and a homogenous dose, Equation 2 can be rewritten: (5.3)TD₅₀/₅ = d₁ (3.3 + d₁) (Equation 3), or d₁² + 3.3d₁ – (5.3)TD₅₀/₅ = 0 (Equation 4). Solving for d₁ yields the single dose equivalents listed in the table above. Adapted from Linskey and Johnstone, 2003.

ear fluid pressure is known as hydrops, and is commonly thought to be associated with Ménière syndrome, which is itself associated with hearing loss and dizziness. It is not yet clear, nor is it intuitively obvious, what impact SRS has on this factor, and to date, no systematic studies have been performed it after SRS for VS. On one hand, SRS might theoretically raise inner ear fluid pressure and contribute to hydrops via impairment of endolymphatic fluid flow through the endolymphatic duct or impairment of absorption of endolymphatic fluid through fibrosis of the endolymphatic sac. On the other hand, SRS could theoretically reduce inner ear fluid pressure by impairing production at the level of the stria vascularis in a manner similar to improving glaucoma by impairment of aqueous humor production at the level of the ciliary body. This is an area ripe for further study.

Other postirradiation temporal bone effects that can affect hearing include serous otitis media from weeping of middle ear mucosa and/or obstruction of the Eustachian tubes, ossicular of temporal bone necrosis, and chondromalacia. The TD50/5 2-Gy fraction total doses for each of these end points have been well-established and published. Using the linear quadratic formula with the assistance of Professor Fowler himself to calculated the biologically equivalent dose for single-dose SRS, and then comparing this result to data obtained from temporal bone sampling during GKS for VS, we were able to show that the SRS dose did not come close to delivering a biologically equivalent dose for these TD50/5 risks (Tables 5 and 6). As a result, these structures are highly unlikely to play a role in hearing loss after SRS for VS.

Conclusions

Our first responsibility to patients undergoing SRS for VS is assurance of permanent tumor control. The best data to date suggest that this is most likely to occur with single-dose SRS and the largest volume of data for this effectiveness exists for the GKS technique. However, maximizing the chances of hearing preservation with GKS for VS is no longer a simple matter of tumor dose selection. Radiosurgery practitioners will serve their patients best by paying careful attention to excluding the cranial nerves from the tumor target volume, limiting dose to a maximum of 12 Gy, carefully insuring 3D treatment conformationality, limiting the VCN dose to < 9 Gy, and limiting cochlea dose as much as possible (ideally < 4–5.33 Gy), with particular attention paid to the inferior basal turn and the modiolus. Future studies should include a more sophisticated analysis of differential frequency loss after SRS to try and differentiate VCN versus cochlea effects as well as explore the potential contribution of changes in inner ear endolymph and perilymph fluid dynamics.

Disclaimer

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

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