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Dosimetric Analysis of Neural and Vascular Structures in Skull Base Tumors Treated with Stereotactic Radiosurgery

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Abstract

Objective. To examine the relationship between the prescribed target dose and the dose to healthy neurovascular structures in patients with vestibular schwannomas treated with stereotactic radiosurgery (SRS).

Study Design. Case series with chart review.

Setting. SRS center from 2011 to 2013.

Subjects. Twenty patients with vestibular schwannomas treated at the center from 2011 to 2013.

Methods. Twenty patients with vestibular schwannomas were included. The average radiation dose delivered to healthy neurovascular structures (eg, carotid artery, basilar artery, facial nerve, trigeminal nerve, and cochlea) was analyzed.

Results. Twenty patients with vestibular schwannomas who were treated with fused computed tomography/magnetic resonance imaging–guided SRS were included in the study. The prescribed dose ranged from 10.58 to 17.40 Gy over 1 to 3 hypofractions to cover 95% of the target tumor volume. The mean dose to the carotid artery was 5.66 Gy (95% confidence interval [CI], 4.53-6.80 Gy), anterior inferior cerebellar artery was 8.70 Gy (95% CI, 4.54-12.86 Gy), intratemporal facial nerve was 3.76 Gy (95% CI, 3.04-4.08 Gy), trigeminal nerve was 5.21 Gy (95% CI, 3.31-7.11 Gy), and the cochlea was 8.70 Gy (95% CI, 7.81-9.59 Gy).

Conclusions. SRS for certain vestibular schwannomas can expose the anterior inferior cerebellar artery (AICA) and carotid artery to radiation doses that can potentially initiate atherosclerotic processes. The higher doses to the AICA and carotid artery correlated with increasing tumor volume. The dose delivered to other structures such as the cochlea and intratemporal facial nerve appears to be lower and much less likely to cause immediate complications when shielded.

Keywords

stereotactic radiosurgery, skull base tumors, dosimetric analysis

Radiosurgery has been increasingly used over the past decade in the management of vestibular schwannomas and other skull base tumors. While improvements in stereotactic radiosurgery (SRS) have allowed for more precise dosing to tumors, the extent of exposure of some surrounding healthy structures as a result of radiation of vestibular schwannomas has not been well described.

Histological examination of experimental animal models after high-dose radiation has demonstrated pathological changes to the middle ear, inner ear, and skull base structures.[1-3] Patients receiving radiation therapy for skull base tumors have been also shown to develop accelerated atherosclerosis and cranial nerve palsies such as facial paresthesias and weakness, as well as hearing loss, tinnitus, and imbalance, partly due to radiation exposure of healthy neurovascular structures of the skull base.[4] Although better than microsurgery, the long-term quality of life in patients with vestibular schwannoma treated with SRS has been shown to be reduced due to ongoing headaches, dizziness, hearing loss, facial nerve weakness, and tinnitus.[5] Thus, understanding the radiation dose to the surrounding structures during SRS can improve pretreatment patient counseling.

A few studies have measured the GammaKnife (GK) radiation dosage to certain skull base, inner ear, middle ear, and external ear structures.[6-10] However, to our knowledge, no studies to date have evaluated the amount of radiation that healthy neural and vascular structures receive after SRS. We aimed to evaluate the radiation doses delivered to healthy neural and vascular structures of the skull base and inner ear in patients treated for vestibular schwannomas.

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Table 1. Neurovascular Structures Evaluated.

No.	Structure
1	Carotid artery proximal portion
2	Carotid artery midportion
3	Carotid artery distal portion
4	Carotid artery vertical portion
5	Basilar artery
6	Anterior inferior cerebellar artery
7	Fifth nerve cisternal
8	Fifth nerve temporal
9	Sixth nerve
10	Facial nerve: labyrinthine segment
11	Facial nerve: geniculate
12	Facial nerve: middle ear
13	Facial nerve: mastoid portion
14	Facial nerve: cisternal
15	Facial nerve mean: total
16	Eighth nerve cisternal
17	Ninth nerve cisternal
18	Cochlear aqueduct: midportion
19	Cochlear aqueduct
20	Cochlea: basal turn
21	Cochlea: basal turn opposite end
22	Cochlea: middle turn
23	Cochlea: apex

Methods

After institutional review board approval was obtained at the University of California–Irvine, a retrospective analysis of 20 consecutive patients with cerebellopontine angle tumors was performed. These patients were all managed by the senior author with assistance from the radiation oncology and physician team via primary SRS between 2011 and 2013. All treatment plans were evaluated in the planning software, using a dose sampling protocol, for each of the structures listed in **Table 1**. Treatment planning was performed with the Accuray Cyberknife Multiple Treatment Planning System (Sunnyvale, CA). The normal structures evaluated were identified by 2 authors independently and confirmed by the senior author on computed tomography (CT), magnetic resonance imaging (MRI), or fusion images.

The radiation to the vessels was measured at the wall in various portions of the carotid artery in the petrous portion, as demonstrated in **Table 1**. The horizontal carotid was divided into 3 segments: proximal, mid, and distal. The proximal, mid, and distal sections of the horizontal carotid artery were defined as the wall of the proximal-most portion of the artery near the cochlea, the midpoint on the same axial cut toward the nasopharynx, and the distal-most portion on the same cut near the nasopharynx, respectively. The vertical segment was defined at the point right before the transition of the vertical to horizontal carotid. Radiation dosage to the anterior inferior cerebellar artery (AICA) was also measured as the closest portion of the vessel near the facial nerve in the cerebellopontine angle at the mid–internal auditory canal (IAC) level on axial cuts. We were unable to identify AICA in all patients. The basilar artery was found and measured at the level of the IAC as well.

All neural structures were measured at their midpoint, with the cursor on the midportion of the structure. The dose to the trigeminal nerve was measured after its exit from the pons on axial cuts, as well as after the prepontine cistern in the distal temporal portion. The abducens nerve was measured medial to the facial nerve. The facial nerve was measured at several points, beginning with the proximal cisternal portion (when not adherent to the tumor) and in the labyrinthine segment. In addition, the radiation to the facial nerve was also measured at the cisternal portion, when possible, at the geniculate ganglion, the tympanic segment at the oval window, and the mastoid segment at the level of the basal turn of the cochlea. We were unable to consistently measure the cisternal portion of the facial nerve due to the tumor proximity to the nerve in certain cases. The glossopharyngeal nerve was measured on axial cuts just lateral to the eighth nerve complex. Similarly, the cochlear radiation was measured on the walls of the basal turn at the round window, the distal basal turn, the middle turn, and the apex.

The distance between the tumor's lateral end and the fundus of the IAC was measured (cerebrospinal fluid [CSF] cap). This distance was correlated with the radiation dose to the labyrinthine segment of the facial nerve, the mean dose to the facial nerve, and the cochlear dose using a linear regression. Tumor volume was correlated with the average dose to the carotid artery and AICA using an adjusted R^2 linear regression. A P value of $<.05$ was considered statistically significant.

Results

Twenty patients with vestibular schwannomas who were managed at our SRS center from 2011 to 2013 were included in this study. There were 8 female and 12 male patients. Thirteen of the 20 patients had right-sided tumors. The minimum dose delivered to 95% of tumor volume was 15.49 Gy, delivered over 3 hypofractions in most patients, with only 1 patient receiving unfractionated therapy. Generally, the dose per fraction was set at a mean of 6.35 Gy, with an average treatment duration of 36.4 minutes. The average total tumor size was 16.2 mm (length, including the IAC) × 11.8 mm (parallel to the petrous face) × 10.5 mm (craniocaudal). The tumor sizes range length was (6.4 – 27.6 mm) × (4.6 – 26.3 mm) × (4.6 – 22.1 mm). The average tumor volume was 1227 mm^3 (range, 203-6335 mm^3).

As seen in **Table 2**, all portions of the carotid artery evaluated received a mean radiation dose of less than 6.77 Gy, with the overall average radiation dose delivered of 5.66 Gy. However, there was an extensive range seen among the patients, ranging from 0.36 to 13.0 Gy with a 95% confidence interval (CI) of 4.53 to 6.80 Gy. Such a

Table 2. Radiation to Vascular Structures.

Structure	Mean (SD), Gy	95% Confidence Interval
Carotid artery	5.67	4.53-6.80
Proximal portion	6.79 (3.05)	
Midportion	5.86 (3.18)	
Distal	4.01 (2.90)	
Vertical	6.17 (3.73)	
Basilar artery	2.05 (1.59)	1.33-2.78
Anterior inferior cerebellar artery	8.70 (5.74)	4.54-12.86

Table 3. Radiation to Cranial Nerves.

Structure	Mean (SD), Gy
Trigeminal nerve	
Cisternal	7.73 (5.65)
Temporal	2.69 (2.18)
Abducens nerve	2.97 (2.44)
Facial nerve	
Labyrinthine segment	10.46 (4.83)
Geniculate	3.76 (2.38)
Middle ear	5.42 (3.55)
Mastoid portion	4.49 (4.87)
Cisternal	12.07 (6.42)
Mean total	3.76 (2.95)
Eighth nerve cisternal	11.74 (6.07)
Ninth nerve cisternal	8.22 (6.66)

variation was seen in nearly all the structures evaluated, as seen in **Tables 3** and **4**. Tumor volume demonstrated a statistically significant positive correlation with the radiation dose to both the carotid artery (adjusted $R^2 = 0.556$, $P < .001$) and the AICA (adjusted $R^2 = 0.461$, $P = .038$). This correlation is demonstrated in **Figure 1**. The mean doses to the cochlea (adjusted $R^2 = 0.042$, $P = .563$) and the facial nerve (adjusted $R^2 = 0.058$, $P = .729$) demonstrated no correlation. Overall, the middle turn of the cochlea received the highest radiation dose (mean [SD], 9.37 [2.99] Gy), compared with the basal turn at the round window (mean [SD], 7.55 [3.63] Gy), distal (at the second turn junction) basal turn (mean [SD], 8.15 [2.96] Gy), or apex (mean [SD], 8.17 [2.45] Gy). There was no correlation between the distance from the tumor's lateral margin and the fundus of the IAC (CSF cap) and the radiation dose to any of the different portions of the cochlea. There was no correlation between the distance from the tumor's lateral margin and the fundus of the IAC (CSF cap) and the radiation dose to any of the different portions of the cochlea.

Table 4. Radiation to Various Portions of the Cochlea.

Structure	Mean (SD), Gy
Cochlear aqueduct: midportion	10.13 (5.49)
Cochlear aqueduct	10.66 (3.07)
Cochlea	
Basal turn	7.55 (3.63)
Basal turn at second turn junction	8.15 (2.96)
Middle turn	9.37 (2.99)
Apex	8.17 (2.45)
Mean dose to cochlea	8.31

Discussion

With the advent of SRS in the management of vestibular schwannomas, there is an increasing population of patients managed as such. As of 2011, 42% of neurotologists are using SRS to treat vestibular schwannomas.[11] This number is continuing to trend upward, and surgical volume has been decreasing, with 6 additional neurotologists per year opting for SRS in the management of vestibular schwannomas.[12,13] In addition, with the various complications of surgical resection, including those not seen in SRS[14] and the outpatient nature of radiosurgery, many patients are choosing radiosurgery. SRS has proven to be a safe,[15-17] reliable alternative with equivalent or superior results in select patients, despite rare complications.[16,17] New SRS technology delivers precise, calculated dosage with the guidance of fused CT and MRI, which can be hypofractionated. However, SRS, like any radiation modality, has its risks due to radiation dosage to adjacent healthy neurovascular structures. Given the Accuray software's ability to create a more conformal plan vs the isocenter-based plans of GK, we aimed to measure the radiation dose to healthy neurovascular structures with SRS treatment of vestibular schwannomas.

Radiation to arterial walls is known to be a factor in accelerated atherosclerosis.[18,19] Other effects to the arterial system also include luminal occlusion, thrombosis, and premature vessel aging,[20] with small- and medium-size vessels experiencing the greatest radiation damage. Less frequently, complications, such as undiscovered aneurysms, have also been reported in the literature.[21-23] Larger arteries, such as the carotid artery, may also undergo stenosis in patients who have been radiated.[24-26] Typically, dosages even as low as 2 to 8 Gy have been shown to increase the risk of vascular events.[19,27,28] Doses greater than 8 Gy were reached in the carotid artery wall in 7 of our 20 (35%) patients. In addition, we note that the mean radiation dose delivered to the carotid artery correlated to the volume of the tumor, as shown in **Figure 1**. We noted that the average tumor volume was over 4 times as large (2247 mm^3) compared with the other patients who received doses under 8 Gy (514 mm^3). In our cohort, a patient with a tumor less than or equal to 15.1 mm in size received less than 8 Gy to the carotid artery wall, whereas a patient with a tumor greater than or equal to 17.8 mm had

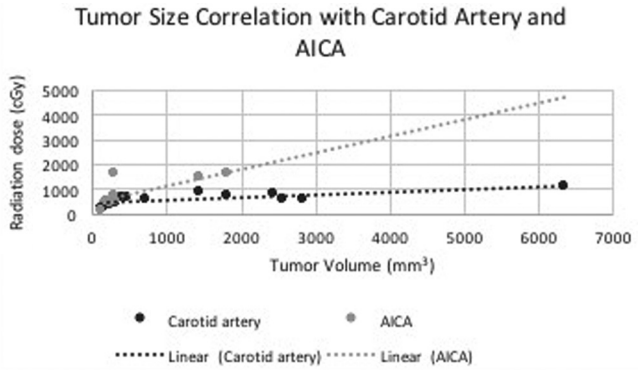

Figure 1. Graph representing the correlation of tumor volume in mm^3 with mean radiation dose to the carotid artery and anterior inferior cerebellar artery (AICA).

radiation doses greater than 8 Gy to the carotid artery wall. Since many of the radiation-induced effects can occur up to 10 years after the inciting event,[29] patients with moderate- or large-size tumors undergoing SRS should be informed about a possible atherosclerosis risk in the future.

Similarly, the AICA was exposed to up to 16 Gy of radiation, and the mean dosage was above the 8 Gy threshold (8.70 Gy). The dose to the AICA also correlated to the tumor volume. The basilar artery exhibited low doses of radiation with a mean dose of 2.05 Gy (95% confidence interval [CI], 1.33-2.78 Gy), exhibiting a low risk of radiation. Given the toxic doses to the carotid artery and AICA, patients, especially younger patients with larger tumors, should be counseled on the risk of atherosclerosis even with short radiation exposure. In addition, we should routinely shield the carotid during the planning to potentially ensure that less than 8 Gy of radiation is given to the carotid. The AICA should ideally be shielded as well.

Cranial nerves also have been previously evaluated in radiation studies and have been shown to have a dose-related effect.[30] The trigeminal nerve has preservation rates of greater than 90%.[30,31] Doses below 12.50 Gy are typically considered safe with an extremely low (0.7%) rate of facial paresthesia or anesthesia; however, they noted that the risk of cranial neuropathy increased by 6-fold for each 2.50-Gy increase over 12.50 Gy.[32] We note that the mean radiation dose to the cisternal portion of the trigeminal nerve was 8.30 Gy and 2.89 Gy for the temporal portion of the trigeminal nerve. In 1 patient with a 27-mm tumor (6355-mm^3 volume), the largest in our series, the radiation dose to the trigeminal nerve exceeded the above threshold, with the highest at 17.09 Gy. Fortunately, that patient did not develop facial paresthesia. In small- to medium-sized tumors, radiation doses to the trigeminal nerve are unlikely to reach toxic levels when treating vestibular schwannomas with SRS.

We were unsuccessful in demonstrating a relationship between the lateral extension of the tumor in the internal auditory canal and the radiation dosages delivered to the facial nerve and the cochlea. This, however, may be an artifact of our small sample size and our active shielding of the cochlea and the intratemporal facial nerve in our planning. Furthermore, considering that the long-term effects of radiation may take 10 or more years to appear, radiosurgery should be considered with caution in patients who are younger and have larger tumors. Potentially, a subtotal resection with radiation for regrowth should be considered in those patients who may be more concerned about facial nerve and vascular outcomes.

Increasingly, neurotologists are opting for SRS in the management of vestibular schwannomas.[11-13] A recent retrospective review of the Surveillance, Epidemiology, and End Results (SEER) database demonstrated an overall shift toward more conservative management of vestibular schwannomas with a decreasing number of patients receiving primary microsurgery.[33] While this article demonstrated a potential toxicity of the AICA and carotid artery with the treatment of tumors, particularly larger ones, SRS has previously been demonstrated as an effective alternative with lower complication rates in select patients.[13,14,34-36] This treatment modality allows for 96% to 99% reported tumor control rates.[37] Tumor control rates are generally better for smaller tumors (Koos grade 1) compared with Koos grade 2 or higher tumors with a hearing preservation rate of 85% and 75%, respectively.[37,38] Despite the possible arterial toxicity presented in our study when treating larger tumors, SRS can allow for good tumor control with high hearing preservation rates and should be strongly considered a treatment option for select patients with vestibular schwannomas.

This study is limited by the small sample size. Another limitation, inherent to all studies of this nature, is that this study analyzes patients treated by a single individual at a single institution. A multi-institutional study of this nature is possible but may introduce some bias when selecting the location for each measurement. We chose those years to ensure adequate follow-up of the patients regarding their facial nerve, trigeminal nerve, and imbalance. Hearing results, we felt, were beyond the scope of this study and will be reported in the future with a larger data set and more long-term follow-up. In addition, data on atherosclerosis development in our patient cohort are lacking. Given the long-term and multifactorial etiology of atherosclerosis, we believe that this issue warrants further study with prospective data gathering with magnetic resonance arteriography.

Conclusions

The evidence from this radiation dosimetry evaluation shows that SRS generally allows for safe radiation dosages to surrounding structures. Patients with tumors that were 17.8 mm or larger received radiation doses of greater than 8 Gy to the carotid artery wall, which can lead to atherosclerosis. Patient with larger tumors received doses of radiation to the AICA that can also lead to atherosclerosis. The dose delivered to other structures, such as the cochlea and facial nerve, appears to be lower and much less likely to cause immediate complications.

Author Contributions

Yarah M. Haidar, contributed to the acquisition and analysis of work, drafting of manuscript, final approval, and agrees to the work integrity; **Jay M. Bhatt**, contributed to the acquisition and

analysis of work, drafting of manuscript, final approval, and agrees to the work integrity; **Yaser Ghavami**, contributed to the acquisition and analysis of work, drafting of manuscript, final approval, and agrees to the work integrity; **Omid Moshtaghi**, contributed to the acquisition and analysis of work, drafting of manuscript, final approval, and agrees to the work integrity; **Amanda Schwer**, contributed to the interpretation of data, revising the work, final approval, and agrees to the work integrity; **Stafford Chenery**, contributed to the acquisition and analysis of work, drafting of manuscript, final approval, and agrees to the work integrity; **Hamid R. Djalilian**, contributed to the interpretation of data, revising the work, final approval, and agrees to the work integrity.

Disclosures

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