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RADIATION THERAPY AND HEARING LOSS

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A review of literature on the development of sensorineural hearing loss after high-dose radiation therapy for head-and-neck tumors and stereotactic radiosurgery or fractionated stereotactic radiotherapy for the treatment of vestibular schwannoma is presented. Because of the small volume of the cochlea a dose–volume analysis is not feasible. Instead, the current literature on the effect of the mean dose received by the cochlea and other treatment- and patient-related factors on outcome are evaluated. Based on the data, a specific threshold dose to cochlea for sensorineural hearing loss cannot be determined; therefore, dose–prescription limits are suggested. A standard for evaluating radiation therapy–associated ototoxicity as well as a detailed approach for scoring toxicity is presented. © 2010 Elsevier Inc.

Radiotherapy, Sensorineural hearing loss, Ototoxicity, Auditory, Ear, QUANTEC.

1. CLINICAL SIGNIFICANCE

Radiation therapy (RT) may damage the cochlea and/or acoustic nerve, leading to sensorineural hearing loss (SNHL) (1–4), with resultant long-lasting compromise in the quality of life. This report focuses on RT-induced SNHL in adults who have received fractionated RT, stereotactic radiosurgery (SRS), and fractionated stereotactic RT (FSRT) for head-and-neck cancers and vestibular schwannomas (VS).

2. ENDPOINTS

SNHL is traditionally defined as a clinically significant increase in bone conduction threshold (BCT) at the key human speech frequencies (0.5–4.0 kHz), as seen in pure-tone audiometry. However, reports of SNHL after fractionated RT vary in terms of: (a) the frequencies evaluated (*e.g.*, 2 or 4 kHz alone (5,6) and/or pure tone average [PTA] of frequencies between 0.5–3.0 kHz) (7–9); (b) the control/standard used for comparison (*e.g.*, pre-RT BCT of same ear (10) or post-RT BCT of the contralateral ear (5), or age-specific standard (4)); and (c) the change in BCT (ΔBCT) that is defined as clinically significant (*e.g.*, 20 dB (5, 6), 15 dB (7, 8), 10 dB (5)). The degree of hearing loss after RT for head-and-neck cancer is worse at higher frequencies, as presented in Figures 1a–c (5–8, 10–12). Although early changes in hearing can be reversible, persistent hearing loss (HL) continues to increase with time (11). Selected studies on SNHL after head-and-neck radiation therapy are shown in Table 1.

Hearing status after SRS for VS is evaluated using the Gardner-Robertson hearing grade (GRHG) scale, which includes both PTA and speech discrimination scores (SDS) (13). HL after SRS for VS is commonly presented as pre-RT to post-RT variation in GRHG as: (a) pretreatment hearing preservation (HP) in terms of (i) serviceable hearing (SH), as hearing that is useful with or without a hearing aid, or (ii) measurable hearing (MH), as any hearing with detectable audiometric responses; and (b) improvement or loss in hearing expressed as change in GRHG. Selected studies on the treatment of vestibular schwannomas are shown in Table 2.

Acute SNHL has been reported after SRS (14), but not after fractionated RT. Hearing impairment has been reported within 3 to 24 months after single-fraction SRS (13, 15), with a median time to onset of 4 months (15, 16). Although it can occur as early as 3 months after completing fractionated RT, the median latency is 1.5–2.0 years (10, 11).

3. CHALLENGES DEFINING VOLUMES

Computed tomography (CT)-magnetic resonance imaging fusion is helpful in defining the inner ear. Its small size and location (embedded deep in the temporal bone) make it challenging to delineate on CT scans and requires the appropriate bone window, level, and image thickness (preferably

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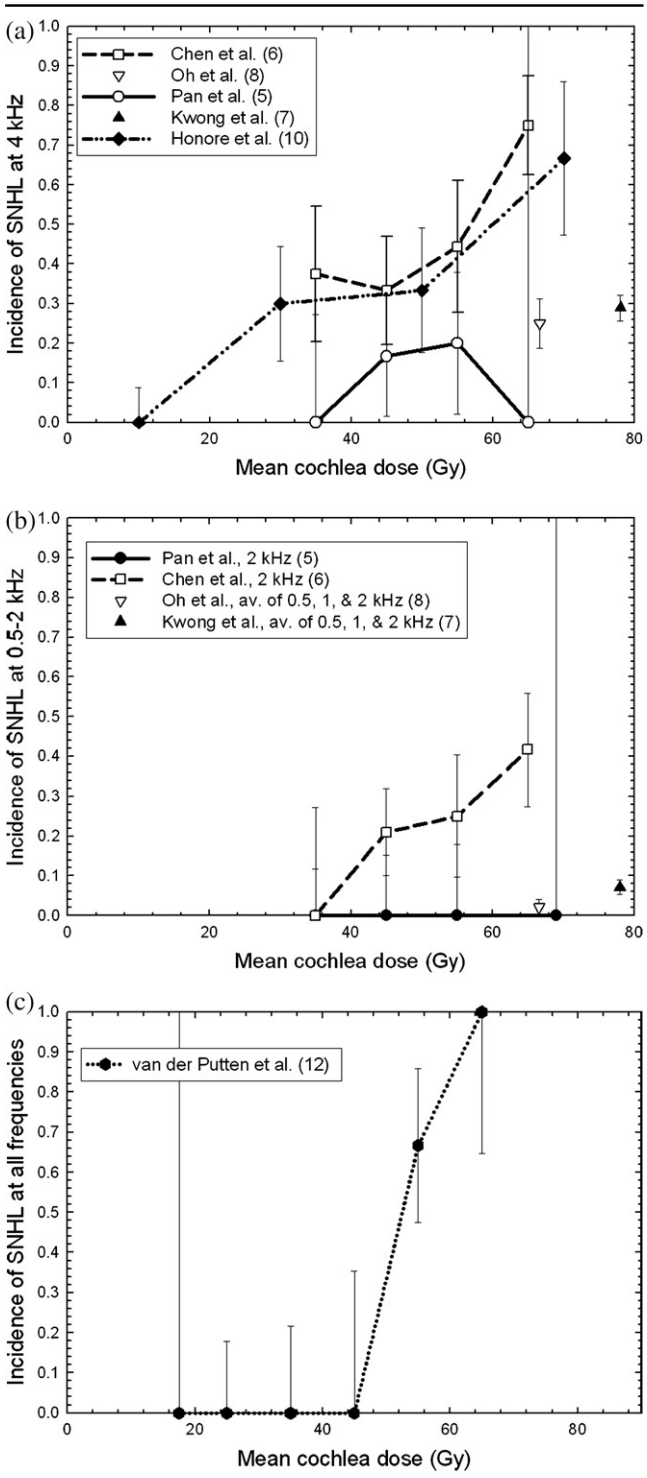

Fig. 1. Mean dose response for sensorineural hearing loss (SNHL) at (a): 4 kHz; (b): 0.5–2 kHz; and (c): all frequencies (0.25–12 kHz). Data from: Figure 3 of Chen *et al.* (6) (retrospective study; SNHL defined as a ≥20-dB increase in the bone-conduction threshold at ≥1 year; patients received concurrent and adjuvant cisplatin chemotherapy); Figure 1 of Honore *et al.* (10) (retrospective study; SNHL defined as 20-dB increase in the bone-conduction threshold at ~0.5–6.5 years); Figure 2 of Pan *et al.* (5) (prospective study; SNHL defined as a 20-dB difference between bone-conduction thresholds for ipsilateral and contralateral ears at 1 year; doses are ipsilateral-ear mean doses minus contralateral-ear mean doses); Table 2 of Oh *et al.* (8) (prospective study; SNHL defined as a 15-dB increase in the bone-conduction threshold at 1 year; patients received neoadjuvant and concurrent cisplatin chemotherapy); Tables 1 and 2 of Kwong *et al.* (7) (prospective study; SNHL defined as a 15-dB increase in the bone-conduction threshold at 1 year; patients received neoadjuvant and concurrent chemotherapy; ears received the full prescription dose; prescriptions were converted to biologically effective dose in 2 Gy fractions using $\alpha/\beta = 3$ Gy); Fig 2 of van der Putten *et al.* (12) (retrospective study; SNHL defined as a 15-dB increase in the average of all pure-tone thresholds at 2–17 years).

≤1.0 mm). The cochlea is a conical structure with its base resting anterior to the internal auditory canal and its apex pointed anteriorly, inferiorly, and laterally, toward the carotid artery. The vestibule is located posterior to the cochlea and lateral to the internal auditory canal. The internal auditory canal is a readily apparent landmark for identification of the cochlea and vestibule on CT (Figure 2). The volume of cochlea can be defined on axial CT images as the net volume defined by the bony labyrinth. In adults, the reported average volume of the cochlea using CT varies from 0.13 mL (range, 0.11–0.15 mL) (17) to 0.56 mL (range, 0.15–0.91 mL) (5).

4. REVIEW OF DOSE–VOLUME DATA

Standard fractionated RT for head-and-neck cancer

A dose–volume analysis is impractical for the cochlea due to its small volume and the limitations associated with its delineation. Several studies have attempted to relate mean or median cochlear dose to persistent hearing loss (6, 10, 18).

Pan (5) prospectively studied BCTs in 31 patients 1–36 months after unilateral RT with standard fractionation using changes seen in the contralateral ear as standard (0.25-8 kHz). ΔBCTs >10 dB were rarely seen unless the corresponding difference in mean cochlear dose was ≥45 Gy. The doses to the contralateral cochlea varied between 0.5 and 31.3 Gy (mean, 4.2 Gy).

Honore (10) retrospectively estimated mean cochlear doses in 20 patients with head-and-neck cancer (1.8–4.3 Gy/fraction) and observed ΔBCT 7–79 months post-RT. Doses were reconstructed from patient-specific CT scans or proxy phantoms. A dose-response relationship was observed for ΔBCT >15 dB at 4 kHz, but not at other frequencies.

Chen (6) retrospectively studied 22 patients treated with RT for nasopharyngeal cancer (with fraction sizes from 1.6–2.3 Gy and concurrent/adjuvant chemotherapy) and studied ΔBCT 12–79 months post-RT. A significant increase in hearing loss (ΔBCT of ≥20 dB at one frequency or ≥10 dB at two consecutive frequencies) was observed for all frequencies (0.5–4 kHz) when the mean dose received by the cochlea was >48 Gy.

Van der Putten (12) retrospectively evaluated ΔBCT 2–7 years after RT in 21 patients with unilateral parotid tumors (fraction sizes 1.8–3.0 Gy). Using the contralateral ear as a control, SNHL (ΔBCT >15 db difference in ≥three frequencies between 0.25–12 kHz) was seen when mean doses received by the cochlea were >50 Gy.

Oh (8) prospectively studied ΔBCTs (0.25–4 kHz) 3–12 months post-RT in 25 patients with nasopharyngeal cancer (fraction size 2 Gy). In this study, the inner ear doses were

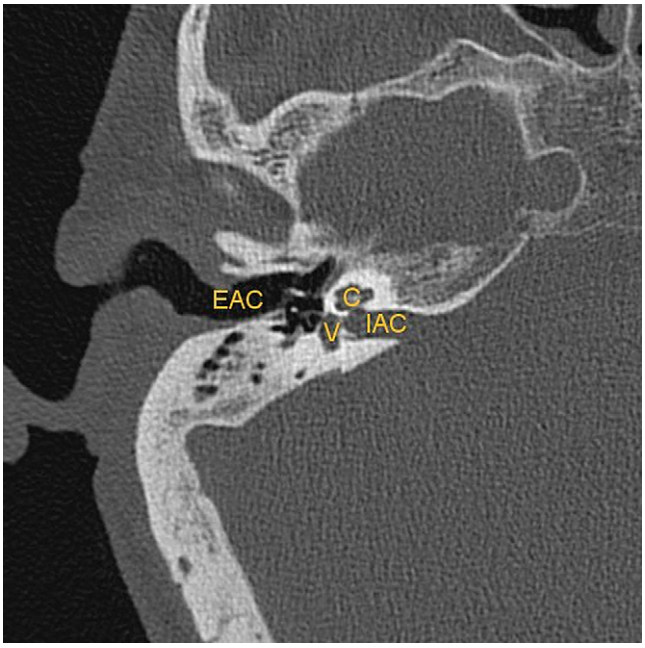

Fig. 2. Axial computed tomography image through the skull base. EAC = external acoustic canal; C = cochlea; V = vestibule; IAC = internal auditory canal.

high (63–70 Gy), and hearing loss (ΔBCT ≥15 db from baseline) was associated with total dose received by the inner ear.

SRS for vestibular schwannomas

Volume–length effect. A dose–volume analysis is not feasible because of the small nerve diameter, lack of visibility on CT, and variable thickness. Nevertheless, the location and length of the cochlear nerve involved with tumor and the prescription/marginal tumor dose reflect the dose received by the cochlear nerve (16, 19). For example, the cochlear nerve may receive less radiation if it lies on the tumor surface vs. if it passes through the core. SRS was found to be more likely to preserve hearing in patients with small VS (<3 cm) vs. larger lesions (20). When SRS is used to treat intracanalicular VS with an irradiated nerve length of 4–12 mm, neither the tumor position in the canal (lateral vs. medial) nor the length of the nerve correlated with long-term hearing preservation. However, the marginal/prescription dose to the tumor was significant as was the dose extending beyond the tumor volume inside the canal was the most important factor responsible for cochlear nerve injury in SRS patients (13). Intracanalicular tumor volume (<100 mm^3 vs. ≥100 mm^3) and intracanalicular integrated dose (dose × volume) are also thought to influence hearing loss (21).

Total dose effect. In one SRS study, patients receiving a mean maximum cochlear nucleus dose in the brain stem of 6.9 Gy and mean cochlear dose of 9.1 Gy retained useful hearing, whereas those in patients with hearing declines received 11.1 Gy and 7.8 Gy (22). In another study, serviceable hearing was preserved in 100% of the patients receiving marginal tumor doses ≤14 Gy but dropped to 20% in those receiving >14 Gy (13). Other studies noted increased hearing preservation with marginal tumor doses of 10–16 (vs. 25) Gy (23), and 12–14 (vs. 16–20) Gy (24, 25).

5. FACTORS AFFECTING RISK

Treatment-related factors

(1) The mean total dose to the cochlea during fractionated RT, or to the eighth cranial nerve in SRS for VS, is a dominant factor in post-RT hearing status (see Review of Dose–volume Data).
(2) The effect of dose per fraction (≤ or >2.0 Gy) has not been thoroughly described.
(3) The one study comparing once-daily vs. twice-daily fractionation observed no effect (4). Some studies suggest that the patients treated for VS with FSRT have a better chance of maintaining serviceable hearing when compared with those treated by SRS (23–25). Hypofractionated RT with four fractions of 5 Gy, or five fractions of 4 Gy, may have less toxicity than SRS in fractions of 10–12 Gy (26).
(4) The possible synergistic toxicity of chemotherapy combined with RT has been studied prospectively (5, 7, 8, 11, 18), and retrospectively (4, 6, 10, 12). Cisplatin is known to cause hearing loss (24). Increased toxicity has been observed in patients treated with both adjuvant and concurrent cisplatin-RT (4, 6, 18). Low (18) reported results at 1 and 2 years after RT delivered with concurrent and adjuvant cisplatin and found significant increases both in BCT at 4 kHz and in BCTs averaged over 0.5, 1, and 2 kHz. Conversely, no such increase has been seen in patients treated with neoadjuvant cisplatin followed by RT (*i.e.*, without concurrent cisplatin/RT) (7, 8, 11).

Patient-related factors

(1) The rate of post-RT SNHL appears to increase with age (>50) (4, 5, 7, 10, 11, 27). Grau (28) found a significant relationship between higher patient age and increased risk of hearing loss, but, when corrected for dose, the correlation disappeared. Higher rates of post-RT SNHL have been reported in males compared with females (7, 11). Other studies have not observed any difference in the incidence of SNHL between sexes or races (4).
(2) Greater post-RT hearing losses (*i.e.*, greater thresholds) have been associated with better pre-RT hearing (*i.e.*, lower thresholds) (5, 10).
(3) Post-RT otitis media has been associated with an increased risk of SNHL (4, 7, 11).
(4) Compared with sporadic VS, VS secondary to neurofibromatosis (NF2) after SRS or FSRT exhibits lower hearing preservation and increased hearing deterioration (23, 29, 30).
(5) Cerebral spinal fluid shunt has been suggested to increase the risk of HL after RT in children and perhaps adults (31).

6. MATHEMATICAL/BIOLOGICAL MODELS

The values of TD5/5 = 60 Gy, TD50/5 = 70 for SNHL suggested by Emami (34) are not supported in the literature and

should not be utilized in treatment planning. Nevertheless, the information on dose–response modeling for post-RT SNHL remains limited.

Pan (5) constructed a linear model demonstrating the differences between pre-RT and post-RT BCTs (corresponding to frequencies varying from 0.25 to 8 kHz) for the ipsilateral and contralateral ears and their association with relative dose scale, age, test frequency, and baseline (*i.e.*, pre-RT) BCT and presented these differences in the form of nomograms. Because of its complexity, the details of the model cannot be presented here (5). In brief, hearing loss was found to depend on frequency tested, age, baseline hearing, and dose to inner ear.

Honore (10) presented a logistic model of the probability of post-RT hearing loss ≥15 dB at 4 kHz, including only dose, which indicated that D_{50} = 48 Gy (95% confidence interval not reported) and γ_{50} = 0.70 (range, 0.22–1.18). Adjusting for patient age and pretreatment hearing level revealed a steeper dose-response curve with γ_{50} = 3.4 (95% confidence interval, 0.3–6.5).

Their multivariate logistic regression model is presented.

$$P = \exp\left(b_0 + \sum_i b_i x_i\right) \Big/ \left[1 + \exp\left(b_0 + \sum_i b_i x_i\right)\right] \quad (1)$$

Where x1 = dose in Gy, x2 = pretreatment hearing threshold in dB, x3 = observation time in years, b0 = -24.9, b1 = 0.30 Gy^{-1} (0.03–0.56), b2 = -0.44 dB^{-1} (-0.86–0.01), and b3 = 0.46 $year^{-1}$ (0.02–0.90) with a p value of <0.05. Honore (10) also modeled a post-RT increase in BCT at 4 kHz with multiple linear regressions. Dose, age, and pretherapeutic hearing level were significant ($p < 0.05$), with the coefficients (95% confidence intervals): 0.31 (±0.15) dB/Gy, 0.53 (±0.21) dB/year, and -0.28 (±0.22) dB/dB, respectively. The constant shift in hearing level in this model, -21.6 (±11.2) dB, was relatively large.

Chen (6) constructed linear models for post-RT changes in BCTs at frequencies between 0.5 and 4 kHz and found that dose was significant at all frequencies. In a multivariate linear model, RT dose, number of cycles of cisplatin, and time to post-RT hearing test were significant at 4 kHz. At 2 and 3 kHz, RT dose and time to posttreatment hearing test were significant. At 1 kHz, only RT dose was significant. In addition, hearing loss in the opposite ear was seen to be highly significant, which may provide additional evidence of the toxicity of concurrent plus adjuvant cisplatin.

Van der Putten (12) fitted an NTCP model to the incidence of asymmetrical SNHL (with a minimum of three frequencies from 0.25–12 kHz) as a function of mean dose to the ipsilateral inner ear and obtained D_{50} = 53.2 Gy with γ50 of 2.74 and D_{10} = 42 Gy.

The incidence of hearing loss at 4 and 2 kHz as reported by Honore (10), Chen (6), and Pan (5) are shown in Figures 1a and 1b. The data of Van der Putten (12), on hearing loss at combined frequencies, are shown for comparison in Figure 1c. The sources for these data and caveats concerning the comparisons implied by these plots are given in the figure legend. It is clear that the response seen by Pan (5) is considerably smaller than that seen by the other studies. This could be due to a number of factors, the most obvious being the relative endpoint and relative dose scale used by Pan, and the influence of chemotherapy in Chen (6). However, the complication rate seen by Honore (10) (in patients treated without chemotherapy) is of the same order as that of Chen (6).

Flickinger (19) modeled the effects of minimum tumor dose D_{min} and transverse tumor diameter (Td) with multivariate logistic regression analysis (equation 1) for the risk of acoustic neuropathy (defined as any variation in either PTA or SDS resulting in decline in GRHG for patients with at least Class IV hearing) in patients treated with SRS for VS in two datasets. The coefficients b_1 (1/Gy) for D_{min} were 0.166, 0.158 (with respective p = 0.00745, 0.1084; SE_{coeff}, 0.091, 0.097). The coefficients b_2 (1/cm) for Td were 0.752, 0.818 (with respective p = 0.0079, 0.039; SE_{coeff}, 0.276, 0.276). The constants b_0 were -4.57, -4.48 (with respective p = 0.0044, 0.0076; SE_{coeff}, 1.56, 1.64).

In addition to the limited information on modeling SNHL, there remain several limitations in both prospective and retrospective studies in the current literature, such as a relatively small number of patients, variation in the standard for HL, frequencies evaluated, and other approximations (*e.g.*, the use of a proxy phantom in retrospective studies), thereby making the choice of any specific model for routine clinical utilization difficult.

7. SPECIAL SITUATIONS

(1) Data on cisplatin-RT suggest that radiation doses to the cochlea should be strictly limited when delivered with cisplatin.
(2) Data presented may not be applicable to fractionation schedules beyond the ranges studied.
(3) Data presented in this review apply to adult patients only; for data on pediatric patients, see Hua *et al.* (32).
(4) Data for hearing response after SRS or FSRT for sporadic tumors may not be representative of the patients with VS secondary to NF2.

8. RECOMMENDED DOSE–VOLUME LIMITS (WHERE POSSIBLE WHILE RETAINING THE DESIRED TARGET COVERAGE)

(1) For conventionally fractionated RT, to minimize the risk for SNHL, the mean dose to the cochlea should be limited to ≤45 Gy (5, 6) (or more conservatively ≤35 Gy) (10). Because a threshold for SNHL cannot be determined from the present data, to prevent SNHL the dose to the cochlea should be kept as low as possible.
(2) For SRS for VS, the prescription dose should be limited to 12–14 Gy for hearing preservation(24, 25, 33).

Table 1. Selected studies for SNHL after head-and-neck radiation therapy

Author	Number of patients in study	Mean cochlear dose (Gy)/Rx dose (Gy)	Dose per fraction (Gy)	Chemoradiation (cisplatin based)	Influence of variables on the outcome: Chemo-radiation	Age	Post-RT SOM	Gender	Time to hearing test	Pre-RT hearing level	Standard used for comparison	Endpoint for SNHL (shift in BCT)/ frequencies (kHz) tested
Prospective												
Grau *et al.*, 1999 (28)	22	NS/60–68	2–2.81	No, RT alone	—	No*	—	—	No	No	Same ear	Nominal shifts in BCT (in dB) reported/ 0.5, 1.0, 2.0, 4.0
Kwong *et al.*, 1996 (7)	132	NS/71.3–85	2–3.5/2†	Yes‡, neoadjuvant	No	Yes§	Yes	Yes‖	Yes	No	Same ear	15/avg. of 0.5, 1, 2 15; 4
Ho *et al.*, 1999 (11)	294	70–91†/59.9–70	2–3.5/2†	Yes‡, neoadjuvant	No	Yes	—	—	Yes	No	Same ear	10/avg. of (0.5, 1, 2) 10; 4¶
Oh *et al.*, 2004 (8)	32	54.3–81.4/70	2	Yes‡, neoadjuvant and concurrent	No	Yes‡**	Yes	Yes‖	Yes	—	Same ear	15/avg. of (0.5, 1, 2) 15; 4
Pan *et al.*, 2005 (5)	22	Ipsi:‡ 14.1–68.8 Contra:‡ 0.5–31.3/40–70	NS	RT alone (18) Concurrent chemo. (4)	—	Yes	—	No	No	Yes††	Contralateral ear	20/0.25, 0.5, 1, 2¶, 4¶, 8
Low *et al.*, 2006 (18)	115	NS/70	2	Yes‡, concurrent and adjuvant	Yes (4 kHz)	—	—	—	—	—	Same ear	Nominal shifts in BCT (in dB) reported/4, avg. of (0.5, 1.0, 2.0)
Retrospective												
Honore *et al.*, 2002 (10)	20	7.1–68/ 50–68	2–4.3	No, RT alone	—	Yes	—	—	No	Yes††	Same ear	15/0.5, 1, 2, 4 20; 4¶
Chen *et al.*, 2006 (6)	22	28.4–70	1.6–2.34	Yes, concurrent and adjuvant	Yes (4 kHz)	No	No	—	Yes	No	Same ear	20/0.5, 1, 2¶, 3, 4¶
Van der Putten *et al.*,2006 (12)	52	29.2–77.3/50–70	1.8–3.0	No, RT alone	—	—	—	—	—	—	Contralateral	15/0.25–12 for ≥3 of these frequencies

Abbreviations: NS = not specified; AS = absolute shift in the hearing threshold reported; SOM = serous otitis media; RT = radiation therapy; CT = bone conduction threshold; db = decibels; SNHL = sensorineural hearing loss; Rx = prescription.

* Dose and age component of HL separated.

† Total doses calculated as BED in 2 Gy fractions, with $\alpha/\beta = 3$ Gy.

‡ The primary endpoint of a prospective clinical trial.

§ Older age found significant.

‖ Rate of HL male > female.

¶ Data for these endpoints reconstructed from figures for this paper.

** Younger age found significant.

†† Better pre-RT hearing associated with worse post RT HL.

Table 2. Selected studies on the treatment of vestibular schwannomas

Author and year	No. of patients in study	Marginal tumor dose (Gy)*	Follow-up	Tumor control (%)	Hearing status (%)
SRS					
Hirsch *et al.*, 1988 (34)	126	18–25	Mean 4.7 y	86	HP: 26
Noren *et al.*, 1993 (35)	Total: 254 NF2: 61	18–20 10–15	1–17 y	Unilateral:94 NF2: 84	HP: 22 Moderate HD: 55 Severe HD: 23
Foote *et al.*, 1995 (36)	36	16–20	2.5–36 mo	100	HP (SH): 10 at 1 y 42 ± 17 at 2 y
Flickinger *et al.*, 1996 (37)	273 CT: 118, MRI: 155	12–20	—	96.48	HL, MRI: 32 ± 7 at 3 y HL, CT: 61 ± 7 at 3 y
Kondziolka *et al.*, 1998 (38)	162	12–20 Mean: 16.6	6–102 mo (60% >5 y)	94	HP (SH): 47 HP (MH): 51
Lunsford *et al.*, 1998 (39)	402	Earlier in series: 17 Later in the series: 12–14	Mean: 36 mo	93	HP: 39 at 5 y HP: 68 at last 5 y
Flickinger *et al.*, 2001 (40)	190	11–18 Median: 13	Median: 30 mo Max: 80 mo	91 at 5 y	HP:74 HI:7
FSRT/HP-FSRT					
Andrews *et al.*, 2001 (23)	GK-SRS: 64 (NF2: 5) FSRT: 46 (NF2: 10)	GK-SRS:12 SRT: 50 (2 Gy/fx)	GK-SRS: 119 ± 67 weeks SRT: 115 ± 96 weeks	GK-SRS: 98 SRT: 97	HP, GK: 33 HP, SRT: 81
Williams *et al.*, 2002 (41)	125	Tumors <3 cm: 25/5 fx Tumors ≥3 cm: 30/10 fx	1.0–5.7 y Median: 1.8 y	100	HP: 46 HL: 36 HI: 18
Meijer *et al.*, 2003 (26)	Total: 37 SRS:12 HPFSRT: 25	SRS: 10–12 HPFSRT: 20–25	12–61 mo Mean: 25 mo	—	HP: 91
Combs *et al.*, 2005 (24)	106	FSRT: 57.6 (1.8 Gy/fx)	3–172 mo	94.3 at 3 y, 93 at 5 y	HP: 94 at 5 y

Abbreviations: SRS = stereotactic radiosurgery; SOM = Serous Otitis Media; HL = hearing loss; MRI = magnetic resonance imaging; BCT = bone conduction threshold; CT = computed tomography; SRT = stereotactic radiotherapy; NF2: neurofibromatosis type 2; FSRT = fractionated SRT; HPFSRT = hypofractionated SRT; HPRT = hypofractionation trial; GRHG = Gardener- Robertson Hearing Grade; HG = hearing grade; HP = hearing preservation corresponding either to serviceable hearing (SH; GRHG-I, II) or measurable hearing (MH; GRHG: III, IV); HD = hearing deterioration; HI = hearing improvement; NR = not reported; UH = useful hearing; GK = gamma knife; fx = fraction; y = year; mo = months.

* Single fraction unless otherwise stated.

(3) A suggested hypofractionation schedule for VS, to provide likely tumor control and preserve hearing, is a total prescription dose of 21–30 Gy in 3–7 Gy per fraction over 3–10 days, though data on this schedule are limited.

9. FUTURE TOXICITY STUDIES

(1) Larger single and multi-institutional prospective trials utilizing pre- and posttreatment hearing tests are required to establish absolute hearing loss as a function of frequency and the absolute radiation dose received by each cochlea, and verify the reported observations regarding SNHL after RT for head-and-neck cancers.
(2) The response of SNHL to chemoradiation needs to be determined in prospective trials as a function of both cisplatin and radiation doses as well as chemo-regimen (neoadjuvant, concurrent, or adjuvant).
(3) In the treatment of VS, the effects of fractionation (SRS vs. FSRT with standard fractionation and hypofractionation), the location and length of the acoustic nerve relative to the tumor, and doses received by it, require systematic prospective investigation.

10. TOXICITY SCORING

Existing scoring systems (*e.g.*, Radiation Therapy Oncology Group, Late Effects on Normal Tissues / Subjective, Objective, Management and Analytic, National Cancer Institute Common Terminology Criteria for Adverse Events) have limitations. We make the following recommendations for coding toxicity.

SNHL after fractionated RT for head-and-neck cancers

(1) Hearing loss should be determined through pre- and post-RT audiometric evaluations of the same ear. In

retrospective studies, if pre-RT audiometric evaluations for the ipsilateral ears are not available, the contralateral ear may be preferable to an age-specific standard, but both should be viewed as substandard relative to pre-RT ipsilateral data.

(2) To avoid transient post-RT hearing fluctuations, hearing should be tested starting 6 months post-RT and at least biannually thereafter.

(3) SDS and four-frequency (0.5, 1.0, 2.0, and 3.0 kHz) bone conduction pure tone average should be used, as endorsed by the American Academy of Otolaryngology-Head and Neck Surgery Committee on Hearing and Equilibrium (9).

(4) For high-frequency HL, 6 kHz bone conduction thresholds should be measured, because a) the basal turn of the cochlea (*i.e.*, highest frequencies) are the first to be affected, b) 6 kHz is highest frequency bone conduction threshold measured with standard bone conducting transducers, and c) bone conduction thresholds minimize the influence of concomitant middle and external ear pathology.

(5) Additionally, a measurement at 4 kHz may facilitate comparison with the present datasets.

(6) ''Clinically significant hearing loss'' should be considered as an increase in the threshold of 10 dB in post-RT BCT, or a decline of 10% in an SDS evaluation, as assessed by an expert.

(7) Clinically significant HL observed in two consecutive PTA evaluations is considered as persistent.

Toxicity scoring after RT for VS

(1) Preservation of pretreatment hearing level: (a) preservation pre-RT GRHG I-IV hearing or (b) in pre-RT GRHG V patients, with no speech discrimination but testable PTA, a preservation of PTA scores.

(2) SH (corresponding to GRHG I-II); commonly defined as PTA $\leq$ 0 and SDS $\geq$50%.

(3) MH is any hearing with detectable audiometric response.

(4) Either an improvement or loss in hearing expressed as a change in GRHG.

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