INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY • BIOLOGY • PHYSICS
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PENTEC ORGAN SYSTEM REVIEW

Modeling the Risk of Hearing Loss From Radiation Therapy in Childhood Cancer Survivors: A PENTEC Comprehensive Review

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Received Feb 27, 2023; Accepted for publication Aug 6, 2023

Purpose: The Pediatric Normal Tissue Effects in the Clinic (PENTEC) hearing loss (HL) task force reviewed investigations on cochlear radiation dose-response relationships and risk factors for developing HL. Evidence-based dose-response data are quantified to guide treatment planning.

Methods and Materials: A systematic review of the literature was performed to correlate HL with cochlear dosimetry. HL was considered present if a threshold exceeded 20 dB at any frequency. Radiation dose, ototoxic chemotherapy exposure, hearing profile including frequency spectra, interval to HL, and age at radiation therapy (RT) were analyzed.

Results: Literature was systematically reviewed from 1970 to 2021. This resulted in 739 abstracts; 19 met inclusion for meta-analysis, and 4 included data amenable to statistical modeling. These 4 studies included 457 cochleas at risk in patients treated with RT without chemotherapy, and 398 cochlea treated with chemotherapy. The incidence and severity of cochlear HL from RT exposure alone is related to dose and age. Risk of HL was <5% in cochlea receiving a mean dose ≤35 Gy but increased to 30% at 50 Gy. HL risk ranged from 25% to 40% in children under the age of 5 years at diagnosis, declining to 10% in older children for any radiation dose. Probability of similar severe HL occurred at doses 18.3 Gy higher for children <3 versus >3 years of age. High-frequency HL was most common, with average onset occurring 3.6 years (range, 0.4-13.2 years) after RT. Exposure to platinum-based chemotherapies added to the rates of HL at a given cochlear dose level, with 300 mg/m^2 shifting the dose response by 7 Gy.

Conclusions: In children treated with RT alone, risk of HL was low for cochlear dose <35 Gy and rose when dose exceeded 35 Gy without clear RT dose dependence. High-frequency HL was most prevalent, but all frequencies were affected. Children

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Presented in part at a special scientific session at the 2019 American Society for Radiation Oncology annual meeting.

Disclosures: None of the authors have conflicts of interest to disclose relevant to this paper.

Acknowledgments—The authors thank the American Association of Physicists in Medicine for logistical support and the PENTEC Steering Committee for guidance and feedback on this project.

Int J Radiation Oncol Biol Phys, Vol. 119, No. 2, pp. 446–456, 2024
0360-3016/$ - see front matter Published by Elsevier Inc.
https://doi.org/10.1016/j.ijrobp.2023.08.016

younger than 5 years were at highest risk of developing HL, although independent effects of dose and age were not fully elucidated. Future reports with more granular data are needed to better delineate time to onset of HL and the effects of chemoradiotherapy. Published by Elsevier Inc.

Introduction

Although radiation therapy (RT) is often an essential component of cure for pediatric tumors of the brain and head and neck region, radiation exposure to auditory structures can adversely affect hearing. Hearing loss (HL) acquired at a young age has been correlated with impaired speech and language development, neurocognitive outcomes, social functioning, and quality of life.[1,2] RT to any portion of the auditory structures including the external, middle, and inner ear as well as the central auditory pathways can lead to conductive, sensorineural, or mixed HL.[3] Radiation dose to the cochlea is used to quantify the effect of radiation on sensorineural HL and will be the focus of this systematic review by the Pediatric Normal Tissue Effects in the Clinic (PENTEC) HL task force. Additional clinical features such as age at RT, platinum-based chemotherapy exposure, and other host factors that can modify risk of HL related to RT will also be discussed.

Anatomy and Clinical Significance

Structures associated with hearing are typically divided into the external ear, middle ear, inner ear, and auditory nervous system. The external ear includes the air-filled cavity that is lateral to the tympanic membrane, and the middle ear is the fluid-filled compartment medial to the tympanic membrane. Sound is transmitted through these areas via mechanical conduction. The inner ear includes the cochlea and the semicircular canals. Damage to any of these structures can cause HL.

Damage to the external or middle ear (eg, from infections or physical pressure) can cause conductive HL. These changes are often reversible. Damage to the inner ear causes sensorineural HL that is irreversible. Radiation can cause damage to any portion of the auditory track.

It is often challenging to ascribe HL solely to RT because many children also receive ototoxic chemotherapy and supportive care medications. In addition, children can have hydrocephalus and/or shunts that can also affect hearing, but this is a finding that is inconsistent across studies and remains an area of research.[4] Typically, chemo-associated HL is bilateral where RT-associated HL can be either bilateral (eg, from whole brain RT for leukemia or medulloblastoma), or unilateral (eg, from RT directed to a portion of the brain or head/neck).

Data from multiple studies consistently show an age-dependence regarding the severity of HL after receiving RT. Notably, younger patients are also at higher risk of HL when exposed to ototoxic chemotherapies.[5–9] The explanation as to why children exposed to ototoxic agents or RT at younger ages are more susceptible to damage from remains unclear.

Endpoints and Toxicity Scoring

There are multiple scales that were largely created to capture the ototoxicity most frequently seen with cisplatin/carboplatin exposure. These often use an ordinal scale from 0 (no complications) to 4 (severe complications). Since the scales used vary across publications, the HL data for this PENTEC review were considered as a Boolean variable, categorized as either present or absent, and defined as a hearing threshold in any of the frequencies of >20 dB. Some of the more commonly used hearing toxicity scales are summarized in Table 1. An endpoint less consistently reported than HL at specific thresholds is HL resulting in the need for hearing aids, typically captured by self-report among childhood cancer survivors.

Hearing loss from ototoxic chemotherapy usually affects the higher, but less often low frequencies. Thus, deficits in low frequencies are commonly not included in grading schemas. Interestingly, HL from RT can involve lower frequencies, and thus current grading scales are inadequate to fully capture (may underestimate) RT-associated HL (Fig. 1). Therefore, we advocate for a new, comprehensive ototoxicity grading scale for use in children and adults treated with cranial RT with or without platinum-based chemotherapy exposure. The comprehensive ototoxicity grading scale is a modification of the International Society of Paediatric Oncology (SIOP) HL scale that includes criteria for low frequency HL and was presented at the American Society for Radiation Oncology and applied in the Massachusetts General Hospital cohort. It is currently being validated in a larger St. Jude cohort (personal communication, J.K. Bass, 2023).

Defining Volumes: Pediatric Imaging Issues

For routine radiation planning, computed tomography (CT) slice thickness of 1 to 2 mm is usually sufficient to delineate the cochlea; thicker-sliced scans are usually of insufficient resolution to delineate cochlear substructures. Contouring atlases are available to help delineate the cochlea as a planning organ-at risk volume.[10–12]

If a more precise localization of the cochlea is needed, high-resolution CT of the temporal bones may be helpful. Axial CT images from the top of the petrous bone to the inferior tip of the mastoid bone with as little as 0.3 mm scan thickness may be optimal with reconstruction into both sagittal and coronal planes. Images should be reviewed with a small field of view and high-resolution bone window settings (Fig. 2). T2 sequences of magnetic resonance imaging also are helpful to delineate the cochlea, which appears bright on T2-weighted images.

Table 1 Hearing loss grading scales

Chang	SIOP	POG	CTCAE version 5 criteria	Brock
Grade 0: ≤20 dB at 1, 2, and 4 kHz	Grade 0: ≤20 dB HL at all frequencies	Grade 0: Not defined	Grade 0: Not defined	Grade 0: <40 dB all
Grade 1a: ≥40 dB at any frequency 6-12 kHz Grade 1b: >20 and <40 dB at 4kHz	Grade 1: >20 dB HL (ie, 25 dB HL or greater); SNHL >4 kHz (ie, 6 or 8 kHz)	Grade 1: 20-40 dB loss >4 kHz	Grade 1: Threshold shift >20 dB HL (ie, ≥25 dB HL); SNHL >4 kHz (ie, 6 or 8 kHz) in at least 1 ear	Grade 1: ≥40 dB at 8 kHz
Grade 2a: ≥40 dB at ≥4 kHz Grade 2b: >20 and <40 dB at any frequency <4 kHz	Grade 2: >20 dB HL; SNHL at ≥4 kHz	Grade 2: >40 dB loss at 4 kHz	Grade 2: Threshold shift >20 dB at 4 kHz in at least 1 ear	Grade 2: ≥40 dB at ≥4 kHz
Grade 3: ≥40 dB at ≥2 kHz	Grade 3: >20 dB HL; SNHL at 2 kHz or ≥3000 Hz	Grade 3: >40 dB loss at >2 kHz	HL sufficient to indicate therapeutic intervention, including hearing aids; threshold shift >20 dB at 2 to <4 kHz in at least 1 ear	Grade 3: ≥40 dB at ≥2 kHz
Grade 4: ≥40 dB at ≥1 kHz	Grade 4: >40 dB HL (ie, 45 dB HL or more); SNHL at ≥2 kHz	Grade 4: 40 dB loss at <2 kHz	Grade 4: Audiologic indication for cochlear implant; >40 dB HL (ie, ≥45 dB HL); SNHL at ≥2 kHz	Grade 4: ≥40 dB at ≥1 kHz

Abbreviations: CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; HL = hearing loss; POG = Pediatric Oncology Group; SIOP = International Society of Paediatric Oncology; SNHL = sensorineural hearing loss.

Review of Dose Volume Response Data and Risk Factors

A comprehensive literature search for studies published between 1970 and 2021 reporting incidence of HL and RT dosimetry to the cochlea was performed. Additional pertinent, selected studies published after 2019 are also discussed based on relevance to this PENTEC review. HL task force members including S.B., A.J., B. M., A.H.Z., and T.I.Y. reviewed 739 abstracts. Twenty-nine studies with potentially relevant information were identified for full review. Of these, 19 articles met criteria for inclusion in the meta-analysis (Tables 2 and 3), but only 2 had sufficiently granular data on 457 cochlea that could be incorporated into a statistical regression model after exclusion of patients exposed to platinum chemotherapy. An additional 2 articles had data on cochlear dose in patients also exposed to ototoxic chemotherapy that could be used for subsequent analysis. Data from the patients in Hua et al[13] included 4 to 5 years of follow-up while data from Bass et al[5] included a median follow-up of 9 years on patients exposed to RT alone. Hua et al notes that HL after radiation alone typically starts between years 3 and 5, but some HL can occur late. Keilty et al[8] show that patients treated with both platinum-based chemotherapy and radiation have HL manifesting earlier than those with RT alone. Bass et al demonstrated that HL can progress with time and yearly audiograms can be helpful to capture that loss.[5] Patients in Scobioala et al[14] and Keilty et al[8] included patients with exposures to both RT and chemotherapy and the audiogram follow-up is 2.5 and 3.1 years, respectively. Additional pertinent, selected studies published after 2019 are also discussed based on relevance to this PENTEC review.[15]

Dose response

In the logistic regression models the dose response for the probability of complication, p, is calculated as

$$p = \exp(b0 + b1 \times dose)/(1 + \exp[b0 + b1 \times dose])$$

with dose measured in Gy.

The dose for 50% complication probability is −b0/b1, and the slope of the response at that dose is [b1]/4.

The results of the analysis of the pertinent available data are as follows.

Data from Bass et al[5] allow us to construct a dose response model for patients treated without chemotherapy, with median follow-up of 9 years. Risk of HL was <5% in ears receiving a mean dose of ≤35 Gy, but risk increased to approximately 30% at 50 Gy (Fig. 3).

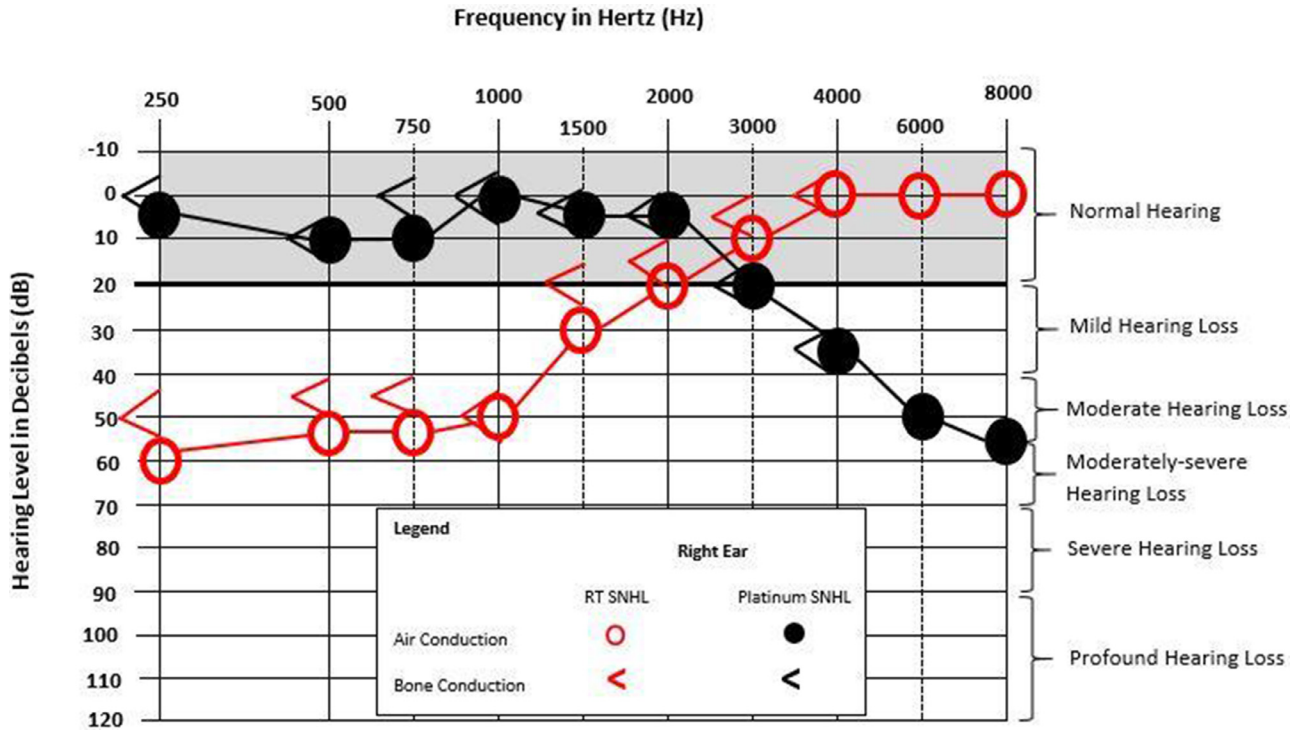

Fig. 1. This figure illustrates a decrease in hearing thresholds for the high-frequency range (4000-8000 Hz) commonly observed after cisplatin therapy (black dots) and a decrease in hearing thresholds for the low- to middle-frequency range (250-1500 Hz) that can occur from radiation therapy (red dots). Thresholds from only 1 ear are displayed. Normal is in the shaded area (above the horizontal), where all frequencies can be heard at ≤20 dB. With injury, the threshold for hearing is increased to >20 dB (ie, below the line, in the unshaded area).

Effect of age

The logistic fit depicted in Fig. 3 with the binned data used resulted in the model coefficients:

$b0 = -5.30 \pm 0.81; b1 = 0.085 \pm 0.017\ \text{Gy}^{-1}$.

The 68% confidence intervals on the binned data are also shown in Fig. 3. This model is based on data from children with a range of ages. Although a multivariate model based on age and dose could not be constructed from the data as reported, the overall rates of HL in children of different ages, and 68% confidence intervals, could be calculated from the data provided (Fig. 4). HL risk ranged from 25% to 40% in children under the age of 5 years whose cochlea was exposed to RT, in contrast to approximately 10% in older children.

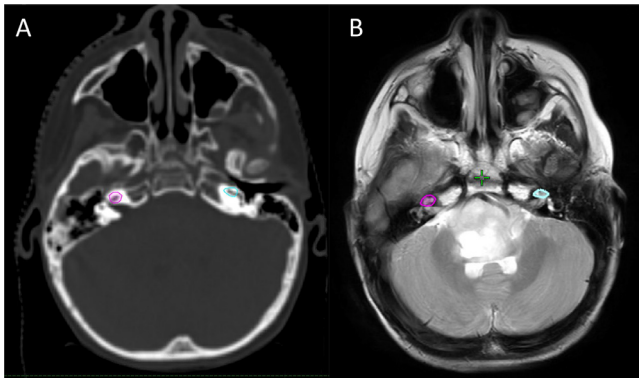

Fig. 2. Delineation of cochlea. (A) The right and left cochlea contoured using the bone window on a computed tomography scan. (B) The right and left cochlea contoured on the T2-weighted sequence of a magnetic resonance image.

Effect of frequency

Hua et al[13] gave scatterplots of dose versus results of hearing tests at different frequencies. This information was used to construct 3 dose responses. The 3 frequency ranges had different dose responses (Fig. 5):

1. At low frequencies (250, 500, and 1000 Hz) the model was

$$b0 = -5.79 \pm 0.88, b1 = 0.0863 \pm 0.0179\ \text{Gy}^{-1}$$

2. At intermediate frequencies (2000, 3000, and 4000 Hz) the model was

$$b0 = -6.85 \pm 1.30, b1 = 0.0990 \pm 0.0249\ \text{Gy}^{-1}$$

3. At high frequencies (6000 and 8000 Hz) the model was

$$b0 = -4.16 \pm 0.67, b1 = 0.0623 \pm 0.0149\ \text{Gy}^{-1}$$

All 3 models were highly significant, with P values $<10^{-4}$.

Table 2 Articles analyzed to guide PENTEC dose constraint recommendations. Articles used for PENTEC dose constraint recommendations

Study	Dose volume factors analyzed	Age analyzed	Dose and age	Significant dose response	Chemotherapy
Bass et al, 2018[16]	Yes	Yes	Yes	No	No
Bass et al, 2016[5]	Yes	Yes	Yes	Yes	No
Hua et al, 2008[13]	Yes	No	No	Yes	No
Moeller et al, 2011[17]	Yes	No	No	Yes	Yes
Paulino et al, 2018[18]	Yes	No	No	No	yes
Paulino et al, 2010[19]	Yes	Yes	No	Yes	Yes
Vieira et al, 2013[20]	Yes	Yes	No	Yes	Yes
Scobioala et al, 2017[14]	Yes	Partial	No	Yes	Yes
Polkinghorn et al, 2011[21]	No	No	No	No	Yes
Liberman et al, 2013[22]	No	No	No	No	Yes
Packer et al, 2003[23]	No	No	No	No	Yes
Paulino et al, 2000[24]	No	No	No	No	Yes
Rednam et al, 2013[25]	No	Yes	Yes	Yes	Yes
Cheuk et al, 2011[26]	No	No	No	No	Yes
Yock et al, 2016[27]	Yes	Yes	Yes	No	Yes
Beyea et al, 2020[7]	Yes	Yes	Yes	Yes	Yes
Cohen-Cutler et al, 2021[28]	Yes	No	No	Yes	Yes
Keilty et al, 2020[8]	Yes	Yes	Yes	Yes	Yes
Trendowski et al, 2021[29]	No	No	No	No	Yes

RT differential effects on frequencies

High-frequency HL was more common than low or intermediate frequency HL for any given cochlear RT exposure (Fig. 5). Average onset of HL was 3.6 years (range, 0.4-13.2) after RT. Scobioala et al provide scatterplots of dose and results of frequency dependent hearing tests in patients treated with conventional fractionation and 560 mg/m^2 of cisplatin chemotherapy. Data from these scatterplots are compared with the frequency dependent results for patients treated without chemotherapy of Hua et al in Fig. 5.[13,14]

As discussed previously, children younger than 5 years were at higher risk for HL after radiation (Fig. 4). No firm associations were found regarding sex, race, use of shunts, or comorbid conditions, although some studies have found associations in these areas.

The additive effect of chemotherapy and radiation

Many studies report on ototoxicity of combined modality chemotherapy and radiation, especially for those who have received cisplatin therapy. Table 3 has been adapted from a literature review of these studies conducted by Paulino et al.[19]

In addition to the modeled data presented previously, a summary of other relevant data is presented here. The study by Keilty et al has excellent data with age and platinum dose; their model predicted that 300 mg/m^2 of cisplatin was equivalent to approximately 7.2 Gy radiation to the cochlea, and that the dose response for the probability of severe HL was shifted to higher doses by 18.3 Gy for patients >3 years of age (vs <3) at treatment (Fig. 6). Their study recommends that for younger patients or children treated with both ototoxic chemotherapy and radiation, keeping cochlear dose to 25 Gy or less is preferable when possible.[8] Keilty et al also found that both cisplatin and carboplatin were additive with RT to risk for HL (as opposed to synergistic). In contrast, Beyea et al[7] did not find carboplatin exposure (as a Boolean variable) to be associated with a risk of HL in a population based study of childhood cancer survivors, but did demonstrate that patients treated with <200 mg/m^2 of cisplatin and patients with <32 Gy of cranial radiation had no elevated risk of needing hearing assistance compared with matched controls.[7] Likely this difference can be explained by the different patient populations, dosimetry capture methods, and different methods used to assign HL status. The study by Keilty et al afforded much more precision with regard to both carboplatin and cisplatin doses as well as cochlear dose. Keilty et al used audiograms and graded them using the SIOP and Chang grading scales, whereas Beyea et al relied on claims submitted for a hearing assistance device. Therefore, Keilty et al would be better equipped to identify HL that did not meet the threshold for

Table 3 Summary of ototoxicity from studies evaluating combined chemotherapy and radiation

Study	No.	Tumor	Estimated cisplatin dose (mg/m^2)	Estimated cochlear RT dose (Gy)	Median audiogram follow-up (mo)	Ototoxicity findings (% if given)
Fouladi et al, 2008[30]	97	MB	300	49 (median)	19	22.7% grade 3-4 ototoxicity
Huang et al, 2002[31]	15	MB	300	36.7 (mean)	18	13% grade 3-4 ototoxicity
Polkinghorn et al, 2011[21]	16	MB	Not stated	53% of prescription boost dose (mean)	12	13% grade 3-4 ototoxicity
Paulino et al, 2010[19]	44	MB	300	35.3 standard risk, 43.0 high risk (median)	41	25% grade 3-4 ototoxicity (18.2% of ears)
Yock et al, 2016[35]	59	MB	348 (median)	30.4 (median)	60	16% grade 3-4 ototoxicity at 5 y
Keilty et al, 2021[8]	171	CNS/H&N	300 (median) (2125 median carboplatin)	40.8 (median, left) 41.2 (median, right)	37.2	Cochlear, cisplatin, and carboplatin dose associated with HL; time since RT also associated
Cohen-Cutler et al, 2021[28]	96	CNS/H&N	326	37.0	25.2	Higher cochlear dose and auto bone marrow transplant associated with HL
Scobioala et al, 2017[14]	29	MB	280 or 560	45-57 Gy	30	90% rate of HL

Abbreviations: CNS = central nervous system; H&N = head and neck; HL = hearing loss; MB = medulloblastoma; RT = radiation therapy.

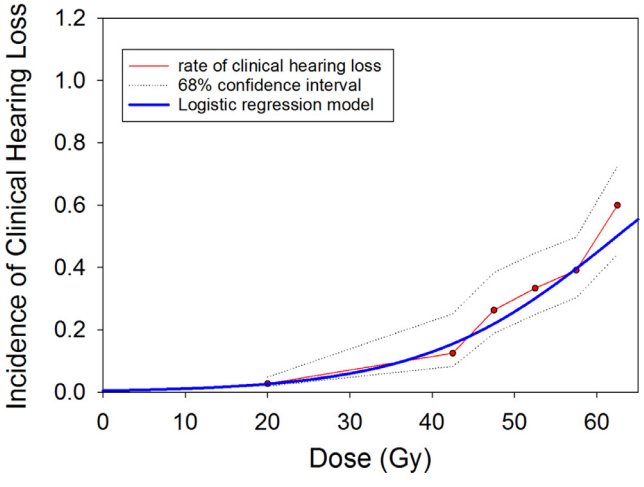

Fig. 3. The incidence of hearing loss due to radiation alone with dose using the best fit model of hearing loss compared with observed rates in quartiles with 68% confidence intervals, plotted at the quartile median dose.[5,13]

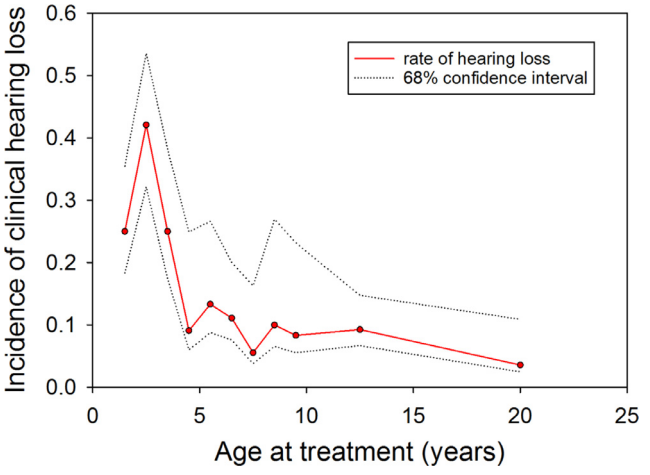

Fig. 4. Variation of the incidence of hearing loss with age at time of treatment, with 68% confidence intervals.[5,13]

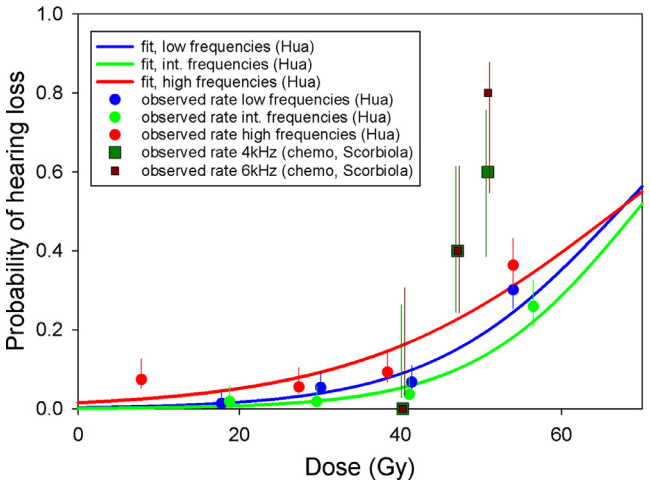

Fig. 5. Frequency and dose dependence of hearing loss using the best fit models for low (250, 0.5, and 1 kHz, blue line), intermediate (2, 3, and 4 kHz, green line), and high frequencies (6 and 8 kHz, red line) are compared with observed rates of hearing loss in quartiles, plotted at the quartile median dose (blue, green, and red circles, respectively).[13] These patients were treated without chemotherapy. Data from Scobioala et al[14] at 4 and 6 kHz (small and large squares respectively) from patients treated with 560 mg/m^2 of cisplatin chemotherapy are included for comparison (squares).

requiring a hearing aid. Furthermore, Beyea et al estimated dose to the ear based on location of the radiation and binned the dose differently (0, 1-32, and 32 Gy) than Keilty et al, who had precise dosimetry to the cochlea.[7,8]

Other relevant data exist that we were unable to incorporate into a unified model because they were insufficient in granularity. Cohen-Cutler et al[28] evaluated the combination of radiation and cisplatin exposure on HL and found that each 10 Gy increase in dose to a cochlea was associated with an odds ratio of 1.64 ($P < .05$) of risk for HL. They found radiation and platinum exposure to be additive, consistent with other studies.[8] They also found that, in this cisplatin and RT treated cohort, exposure to high dose chemotherapy and stem cell rescue (autologous bone marrow transplant) was correlated with a much higher risk of HL compared with those who have not received that dose intensity. They also noted an increased incidence in SIOP grade 2 HL with time from treatment.[28] Moke et al[9] also reported for the first time an independent risk of HL with vincristine chemotherapy, which is commonly used in the pediatric population.

Recommendations for Nominal Dose Volume Goals

The available information reviewed previously has been condensed to provide clinical guidance on appropriate dose limitations for cochlear structures. Given the small volume of cochlear structures, mean dose is recommended as the evaluation metric because minimum and maximum doses or volume doses are not as clinically meaningful. However,

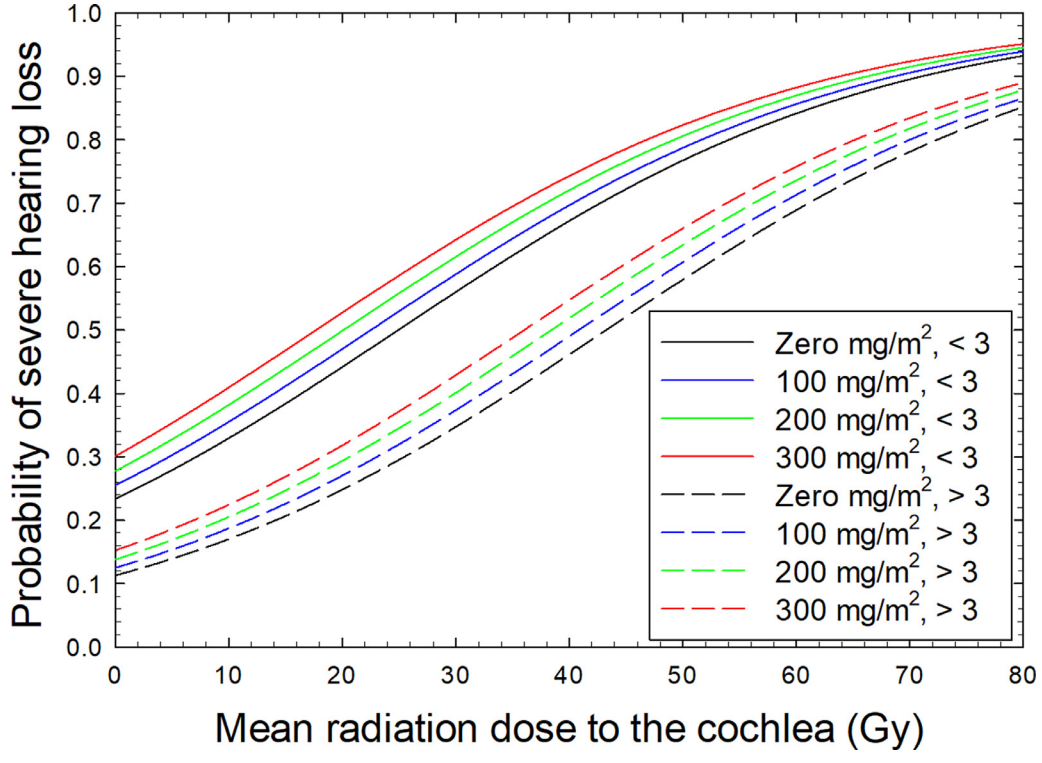

Fig. 6. The radiation dose response for hearing loss 10 years after therapy in children <3 years of age (solid line) or ≥3 years of age (dotted lines) as a function of the chemotherapy dose of Keilty et al.[8]

the article by Cohen-Cutler et al showed that minimum cochlear dose was the most predictive metric associated with sensorineural HL.[28] As in all cases, minimizing exposure to as low as reasonably achievable is the goal. These recommendations are given in light of the need to sometimes accept a potential risk of HL to ensure adequate tumor target coverage and optimize disease control. Thus, when radiation alone is given to children >5 years old, or for any age if the mean cochlear dose is <30 Gy, we anticipate a <5% risk of HL (Figs. 3 and 4). Although the model from the study by Keilty et al (Fig. 6) indicates that age 3 is a better inflection point for this low <5% risk, they also note that at 0 radiation dose and no exposure to platinum-based chemotherapies baseline HL is as high as 23% in the <3 year olds and 11% in the >3 year olds, presumably due to HL from the tumor or the surgery or for other non-cancer-related reasons.[8] In children being treated with chemotherapy and younger than age 3 to 5 years at the time of treatment, a more conservative dose threshold of <25 Gy might be expected to be associated with helping to mitigate the risk of HL.

Our summary indicates that it is better to be more conservative with doses allowed to the cochlea when possible, compared with the QUANTEC findings where mean cochlea doses of ≤45 Gy in adults were associated with a low risk of HL.[32] Note that QUANTEC did suggest that a more conservative dose of ≤35 Gy would be associated with a low risk in children not exposed to cisplatin chemotherapy. However, the risk of HL rises dramatically when cisplatin chemotherapy is given and is especially pronounced in the younger age groups (<3-5 years).

Several limitations to these recommendations exist, including the possible uncertainty associated with the dosimetric modeling used in this analysis. As discussed before, younger age has been correlated with greater sensitivity to HL secondary to both ototoxic chemotherapy and radiation, probably due to a heightened sensitivity of cochlear structures at younger ages. Confounding factors contributing to HL also exist, such as the effect of surgery for tumor control and the need for ventriculoperitoneal shunts.[5] Additionally, different methods and scales for reporting HL are used in the different studies which can diminish the precision of the data upon which the recommendations are made. Many studies use the threshold for recommending hearing aids as the threshold for HL. However, recommendations about hearing aid use take into account the patient's functional status and developmental disorders, as well as degree of HL, and can be quite subjective in nature and differ by practitioner. Table 4 shows the data summary from each reference used for modeling in Figs. 5 and 6. It also provides the sources of dosimetric data and their estimated uncertainty. Dose distribution to a small cochlear volume is inherently subject to large uncertainty due to its high dependency on CT slice resolution, out-of-field dose calculation algorithm, and patient setup accuracy, particularly in the presence of a high dose gradient. Mean doses from uniformly irradiated cranial dose could be estimated within 5%, while a larger

Table 4 Summary of data used for modeling the risk of hearing loss

Study	Endpoints/prevalence	Years treated	Treatment description	Rx dose	Dose metric	Dose binning	Dose source	Dose accuracy estimate
Hua et al, 2008[13]	RT alone SNHL 14% (11 of 78 patients), 11% (17 of 155 ears)	1997-2001	Brain tumor treated by using conformal RT including IMRT 3D CT-based plan University of North Carolina (PLUNC) TPS	54-59.4 Gy in 1.8 Gy/fx	D_{mean} to cochlea (average, 34.8 Gy [0.1-63.5])	D_{mean} in 10-Gy interval (5-Gy increments from 30-60 Gy)	b	2
Bass et al, 2016[5]	RT-alone SNHL 14% (33 of 235 patients), ~10% (46 of ~470 ears)	1997-2010	Localized brain tumor treated using conformal RT 3D CT-based conformal photon RT or IMRT	54 Gy (craniopharyngioma and low-grade glioma) or 54-59.4 Gy (ependymoma) in 1.8 Gy/fx	D_{mean} to cochlea (Mdn, left, 29.5 Gy [0.0-61.7]; right, 28.8 Gy [0.0-63.9])	D_{mean} in 5-Gy interval	b	2
Scobioala et al, 2017[14]	ChemoRT SNHL Bilateral high-frequency SNHL 90% (26 of 29 patients)	2000-2014	Medulloblastoma treated by surgery + CSI/boost + chemotherapy Tomotherapy or combined RT (static CSI and IMRT boost) Tomotherapy: 3D CT-based TomoTPS_v5 Combined RT: no 3D planning, 2D bilateral Rx + 3D CT-based IMRT boost	55 Gy in 1.8 Gy/fx (low risk) or 68 Gy in 1.0 Gy/fx twice a day (high risk)	Tomotherapy: D_{mean} (and D_{max}) to cochlea Combined RT: estimated D_{mean} to cochlea	D_{mean} in 5-Gy interval	b (tomotherapy/IMRT) a (2D CRT CSI)	2 (boost), 1 (CSI)
Keilty et al, 2021[8]	ChemoRT or RT alone SNHL 340 ears from 171 patients	2005-2017	Brain or head and neck tumors treated with 3D CRT, IMRT, or VMAT Exact cochlea doses collected from TPS	Total dose mdn. 55.8 Gy (23.4-78)	D_{mean} to cochlea (mdn. left, 40.8 Gy [0-77.7]; right, 41.2 Gy [0-75.6])	D_{mean} as a continuous variable	b	2

Sources of cochlear dose are categorized as follows: a. Prescribed; b. TPS computed; c. Measured; d. Reconstructed from the anatomic model; e. Other. Accuracy of cochlear doses was estimated as follows: 1. better than 5%; 2. 5% to 10%; 3. 10% to 15%; 4. 15% to 20%; 5. >2.

Abbreviations: 2D = 2-dimensional; 3D = 3-dimensional; CRT = conformal radiation therapy; CSI = craniospinal irradiation; CT = computed tomography; fx = fraction; IMRT = intensity-modulated radiation therapy; mdn. = median; PLUNC = plan Univeristy of North Carolina; RT = radiation therapy; Rx = prescription; SNHL = sensorineural hearing loss; TPS = treatment planning system; VMAT = volumetric modulated arc therapy.

uncertainty (5%-10%) may be estimated from highly conformal dose distributions using 3-dimensional conformal radiotherapy, intensity-modulated radiation therapy (IMRT), or volumetric modulated arc therapy due to the setup certainty.

Toxicity Scoring Recommendations

Radiation therapy exposure to the cochlea can affect hearing across all frequencies. Current scales including the SIOP scale[33] were developed to measure HL associated with ototoxic chemotherapies. As a result, patients with low- to mid-frequency HL can be underestimated with regard to toxicity grade and its implications for function. A potential solution to modify the SIOP hearing scale to include HL at lower frequencies has been proposed and is being validated in a large St. Jude data set.[34] The modified HL criteria can appropriately grade HL across the full spectrum of the conventional frequency range 250 to 8000 Hz (Table 5).

Data Reporting Standards Specific to HL

Published data on radiation-associated HL for pediatric patients are rare and usually do not allow for systematic dosimetric analysis. The difficulty arises from gathering complete data on large patient series requiring longitudinal follow-up; most often the radiation dose data are missing or inadequate. Such data sets are incapable of independently providing dose responses that are clinically significant and thus results from several series must be combined to validate any normal tissue complication probability models that are proposed. Consequently, it is vital that published data sets conform to rigorous reporting standards so their results can be pooled.

Table 5 The Comprehensive Hearing Loss Grading Scale inclusive of all hearing loss at all frequencies that can be seen in radiation-related hearing loss

Grade	Comprehensive Hearing Loss Grading Scale
0	≤20 dB HL at all frequencies
1	>20 dB HL at any frequency above 4 kHz and/or >20 dB HL at any 1 frequency below 6 kHz
2	>20 dB HL at 4 kHz and above and/or >20 dB HL at any 2 frequencies below 4 kHz
3	>20 dB HL at 2 or 3 kHz and above and/or >20 dB HL at 3 or more frequencies below 2 kHz
4	>40 dB HL at 2 kHz and above and/or >40 dB HL at 3 or more frequencies below 2 kHz

Abbreviation: HL = hearing loss.

We propose reporting of the following information in future studies:

- Patient sex and race
- Clinical indication for RT (ie, cancer diagnosis)
- Age when treated with RT
- Prescribed RT dose and dose fractionation
- RT technique (ie, photon-based 2-dimensional, 3-dimensional, IMRT, Volumetric modulated arc therapy; proton therapy [passive scatter, pencil beam/spot scanning])
- Use of image guidance and treatment planning system
- Mean, minimum, and maximum (D0.1cc) cochlear dose (R, L)
- Exposure to supportive ototoxic medications like aminoglycosides
- Use of possible otoprotectants such as sodium thiosulfate or amifostine
- Chemotherapy type and dose used, including whether high doses were used that required stem cell support. Timing with respect to RT and the agents used should be reported.
  - Cisplatin and carboplatin total doses and dose given per cycle are relevant
  - New data indicate that vincristine is also implicated in HL[9]

Frequency of clinical follow-up for late complications of RT:

- Frequency of audiograms: hearing evaluations for survivors receiving 30 Gy or more to the cochlea with or without ototoxic chemotherapy should be performed no later than the end of treatment and annually for children <6 years of age, every other year for children 6 to 12 years of age, and every 5 years for adolescents and young adults >12 years of age according to the International Late Effects of Childhood Cancer Guideline Harmonization Group recommendations for ototoxicity surveillance for survivors of childhood cancer[35]
- Time to development of HL (date of onset from date of radiation treatment start)
- Shunt placement (before or after RT)
- Surgery to the brain or head and neck region
- Number of patients in the study and number of those with or without toxicity
- Standardized grading scale; we propose the comprehensive grading scale (Table 4)

Future Investigations

Reducing the burden of ototoxicity on children with cancer who are exposed to radiation and/or chemotherapy is an active area of research. Much of the work in this area has been done using pharmaceutical protective agents administered during chemotherapy.

Protective agents

Amifostine was one of the earlier agents to be evaluated to protect against chemotherapy-induced HL. In a study of children with average-risk medulloblastoma, amifostine reduced the 1-year HL probability from 37.1% to 14.5%.[30] In a follow-up study from the same research group, amifostine was effective in children treated for average-risk medulloblastoma but not high-risk medulloblastoma.[36] It may be possible that the lack of efficacy of amifostine is due to the use of higher dose craniospinal irradiation in the high-risk cohort, which could negate any potential otoprotective effect of amifostine. Amifostine has not been studied as an otoprotectant against RT-induced HL but could be evaluated in the setting of treatment regimens that include multiple ototoxic agents (radiation and platinum chemotherapy), such as medulloblastoma.

Sodium thiosulfate (STS) has also been investigated as an otoprotectant against chemotherapy-induced HL. In the SIOPEL 6 study of hepatoblastoma, the risk of HL was half with STS administration, with no adverse effect on tumor control.[37] The Children's Oncology Group study ACCL0431 was a phase 3 randomized study evaluating patients receiving cisplatin; the odds ratio for HL was 0.31 in patients who received STS ($P = .0036$), indicating a statistically significant protective effect.[38] The overall survival of patients who received STS trended to inferior outcome (hazard ratio, 2.0; $P = .07$), which illustrates ongoing concerns regarding reduced tumor control with otoprotective agents. However, the detrimental effect on tumor control may be limited to higher-risk patients with disseminated disease, indicating possible utility as an effective and safe otoprotectant among patients with localized cancers. STS has not been evaluated as an otoprotectant against radiation-induced HL. Medulloblastoma, as a tumor requiring multiple ototoxic treatments (platinum-based chemotherapy and radiation), could be a candidate for evaluation of STS against RT-induced HL.

Given the efficacy of amifostine and STS against platinum-induced HL, there is a need to evaluate whether these agents are effective against radiation-induced HL without any loss of treatment efficacy.

RT technologies

Modern RT techniques such as IMRT and protons provide the potential to limit cochlear dose in comparison to those approaches previously used and reported in many studies, although access to proton therapy remains limited.[39] Use of hypofractionation in pediatric patients with brain tumors is uncommon compared with adults, although specific investigation on potential effects of hypofractionation on hearing would become necessary if used in the future.

Oncologists must be more diligent about reporting treatment and follow-up data for their patients, specifically with type and cumulative dose of chemotherapy to delineate specific dosing recommendations. This will help to facilitate recommendations for patients treated concurrently with radiation and ototoxic chemotherapy.

There is growing evidence that the host genome can affect risk of HL from both platinum-based chemotherapies and RT to the cochlea. Different studies have correlated different genes with worse hearing outcomes,[29] such as rs67522722.[40] Other work has identified genetic variations in *ACYP2* (rs1872328) and *PAK4* (cg14010619) as associated with HL in children treated for brain tumors.[41] This could be helpful in the future to provide better personalized decision-making regarding therapeutic choices (eg, chemotherapies, RT techniques, doses).

Conclusion

Radiation exposure to the cochlea is directly associated with HL. Treating oncologists should attempt to minimize the cochlea mean dose as low as reasonably achievable during radiation planning, while maintaining tumor target coverage. The data suggest that a mean cochlea dose threshold of <35 Gy should have low risks of HL in the absence of ototoxic chemotherapy. However, a lower reference, such as 25 Gy might be more appropriate for children less than 5 years of age, or for patients also exposed to ototoxic chemotherapy (cisplatin or carboplatin).

After cochlea irradiation, dose-dependent HL can occur with both higher and lower frequencies (more often with the former). Since losses can occur in the lower frequencies (which are not well captured by grading scales designed for platinum chemotherapy related HL), a modified grading system is proposed for RT-associated HL. Additionally, increased time from exposure to either radiation, ototoxic chemotherapy or both correlates with increasing incidence and severity of HL. Future reports with detailed data using the comprehensive grading scale (referred to previously) are needed to enable analysis of larger cohorts to better understand the effect of radiation on HL. This is especially important in the context of concurrent chemotherapy use along wide age spectrums with varying follow-up periods. Studies to evaluate pharmaceutical radioprotectants and evolving radiation technologies are warranted to limit HL associated with radiation exposure to the cochlea.

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