Auditory Outcomes in Patients Who Received Proton Radiotherapy for Craniopharyngioma

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Purpose: Compared to photon-based radiotherapy, protons deliver less radiation to healthy tissue resulting in the potential reduction of late complications such as sensorineural hearing loss (SNHL). We report early auditory outcomes in children treated with proton radiotherapy (PRT) for craniopharyngioma.

Method: Conventional frequency (CF = 0.25–8.0 kHz) audiometry, extended high-frequency (EHF = 9.0–16.0 kHz) audiometry, distortion product otoacoustic emission (DPOAE) testing, and speech-in-noise (SIN) assessments were prospectively and longitudinally conducted on 74 children with a median of 2 post-PRT evaluations (range, 1–5) per patient. The median age at PRT initiation was 10 years, and median follow-up time was 2 years. Otoxicity was classified using the Chang Ototoxicity Grading Scale (Chang & Chinosornvatana, 2010) and the American Speech-Language-Hearing Association (ASHA) criteria (ASHA, 1994). Comparisons were made between baseline and most recent DPOAE levels, with evidence of ototoxicity based on criterion reductions of ≥ 6 dB. The critical difference values for comparing SIN scores between two conditions (i.e., pre- and post-PRT) were used to determine a significant change between test scores.

Results: At last evaluation, no patients had SNHL in the CF range, and 2 patients had SNHL (Chang Grade 1a) in the EHF range. Based on the ASHA criteria, a decrease in hearing was observed in 0 patients in the CF range alone, in 9 patients in the EHF range alone, and in 15 patients in both the CF and EHF ranges. DPOAE levels decreased at a faster rate at higher versus lower frequencies. For 41 evaluable patients, SIN perception did not decline over time (p = .6463).

Conclusion: At a median follow-up time of 2 years post-PRT, normal hearing was maintained within the CF range. However, subclinical decreases in hearing were observed, particularly in the EHF range and in the DPOAE level; thus, long-term follow-up is recommended to monitor for potential auditory late effects from PRT.

Pediatric craniopharyngioma is a rare, localized, histologically benign neuroepithelial brain tumor that arises near the pituitary gland and the hypothalamus during embryonic development. Although craniopharyngioma is noncancerous and the 5- and 10-year survival rates are higher than 90% (PDQ Pediatric Treatment Editorial Board, 2017), morbidity from the tumor and treatment is substantial. The current therapeutic approach for managing craniopharyngioma includes a maximal tumor resection or partial tumor resection followed by radiotherapy.

Methods of irradiation have evolved over the past four decades with advances in radiation physics and computer technology, leading to greater precision of radiation delivery, dose reduction to normal tissues, and less adverse effects. Conventional three-dimensional methods of photon-based radiotherapy have historically been used to treat a variety of pediatric brain tumors, including craniopharyngioma; however, proton radiotherapy is associated with late effects, such as sensorineural hearing loss (SNHL). Incidence of SNHL has been reported in 14%–27% of children treated with photon radiotherapy and no ototoxic chemotherapy (Bass et al., 2016; Hua, Bass, Khan, Kun, & Merchant, 2008; Williams, Kun, Thompson, Gould, & Stocks, 2005). Onset of SNHL varies across studies, beginning as early as 3 months (Wang, Kuo, Ho, Lee, & Lin, 2004) to 13 years after radiotherapy (Bass et al., 2016); however, SNHL onset typically occurs 3–4 years following radiotherapy (Bass et al., 2016; Hua et al., 2008).

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Proton radiotherapy (PRT) is an advanced method of irradiation currently being investigated in a limited number of institutions for the management of childhood cancer. Although photon- and proton-based radiation techniques offer similar tumor control (Rombi, Vennarini, Vinante, Ravanelli, & Amichetti, 2014), protons enable a reduction in doses delivered to surrounding normal tissues, potentially decreasing acute and late toxicities when compared to photons (Merchant, 2013). Recent studies have demonstrated decreased incidence of SNHL in pediatric patients treated with PRT versus proton radiotherapy for medulloblastoma (Moeller et al., 2011; Yock et al., 2016) and ependymoma (Macdonald et al., 2013).

The traditional assessment for monitoring ototoxicity is measuring pure-tone thresholds within the conventional frequency (CF) range from 0.25 through 8.0 kHz—frequencies that are critical for speech and language acquisition and recognition. Extended high-frequency (EHF) audiometry is the measurement of pure-tone thresholds at frequencies 9.0 through 20.0 kHz. In addition, distortion product oto-acoustic emissions (DPOAEs) are typically used for monitoring ototoxicity, as these measurements can be acquired objectively, and they provide site-specific information regarding the integrity of the outer hair cells (OHC) within the cochlea. A decrease in DPOAE level, a decrease in signal-to-noise ratio (SNR), and/or loss of DPOAE response indicate OHC damage (Gorga et al., 1993).

Radiation to the cochlea causes damage to the cochlear hair cells and surrounding structures, including the basilar membrane, spiral ligament, stria vascularis, spiral ganglion, and cochlear nerve (Bohne, Marks, & Glasgow, 1985; Hoistad et al., 1998). Hair cell destruction typically occurs at the base of the cochlea where high frequencies are encoded resulting in high-frequency SNHL (Bass et al., 2016; Fong, Beste, & Murray, 1995; Hua et al., 2008; Williams et al., 2005). Similarly, platinum-based chemotherapy agents (i.e., cisplatin and carboplatin) also damage cochlear OHC function (Hinojosa, Riggs, Strauss, & Matz, 1995; Saito et al., 1989; Schweitzer et al., 1984; Wright & Schaefer, 1982), with more severe SNHL occurring in the high frequencies (Li, Womer, & Silber, 2004; Schweitzer et al., 1984). Studies in patients treated with platinum chemo-therapies have demonstrated that EHF audiometry and DPOAEs detect evidence of ototoxicity sooner than CF audiometry, potentially serving as a predictor to ototoxic effects before damage occurs in frequencies important for speech and language perception (Bhagat et al., 2010; Fausti et al., 1994; Knight, Kraemer, Winter, & Neuwell, 2007; Littman, Magruder, & Strother, 1998; Lonsbury-Martin & Martin, 2001).

Speech-in-noise (SN) testing is used to assess the functional impact of ototoxicity by evaluating the patient’s ability to comprehend speech (i.e., monosyllabic words or sentences) in the presence of background noise. In a study by Einarsson et al. (2011), patients with cisplatin-induced SNHL had significant difficulty in understanding words in noise, scoring as low as 54% below reference scores for subjects matched for age and degree of SNHL.

Based on these findings, one could hypothesize that (a) postradiation hearing sensitivity in the EHF range would be affected initially and potentially more severely than hearing in the CF range, (b) DPOAEs would exhibit cochlear hair cell damage before SNHL appeared in the CF range, and (c) SN perception would decline from baseline measures. To our knowledge, EHF audiometry, DPOAE, and SIN outcomes have not been reported in patients treated with cranial radiotherapy alone. The objectives of this study were to describe early auditory outcomes in children and adolescents treated with PRT for craniopharyngioma by reporting the incidence, onset, and severity of ototoxicity based on comparisons of CF and EHF pure-tone audiometric thresholds over time, examining changes in DPOAE levels over time, exploring the potential impact PRT has on SIN perception over time, and identifying potential risk factors associated with decreased auditory function.

**Method**

**Patients**

Between 2011 and 2016, 112 children were enrolled in a Phase II trial of radical surgery or limited surgery and PRT for craniopharyngioma. Patients between the ages of 0 and 21 years were eligible for enrollment. Craniopharyngioma was diagnosed by histology, cytology, or neuroimaging. Patients received neither radiotherapy nor potentially ototoxic drugs before enrollment. The trial (ClinicalTrials.gov Identifier: NCT01419067) was approved by the Human Subjects Institutional Review Board at St. Jude Children’s Research Hospital, and informed consent and assent were obtained from all patients/guardians.

Patients underwent either a gross total resection and observation or subtotal resection and PRT. For patients who received PRT, the total prescribed dose for the planning target volume, which contained gross tumor volume plus margins for microscopic diseases and setup uncertainty, was 5,400 centigray (relative biological effectiveness), abbreviated as cGy (RBE), that is, 4,909 cGy × 1.1 RBE, administered at 180 cGy (RBE) per fraction with one fraction per day, five fractions a week, for a period of 6 weeks. Each cochlea was contoured on two consecutive computed tomography images as a circular structure within the temporal bone. Because of the small size, mean dose was calculated to represent the cochlear radiation dose (CRD). During treatment planning, efforts were made to spare the cochlea without jeopardizing tumor coverage. Exclusion criteria included patients not at risk for SNHL with a zero CRD (n = 6), patients with abnormal middle ear function before treatment (n = 4), patients with insufficient audiologic data (i.e., fewer than two evaluations or incomplete testing due to young age, n = 14), and patients taken off the study (n = 14).

**Audiologic Evaluations**

Audiologic evaluations were conducted prior to PRT (baseline) and annually thereafter. Otoscopy and tympanometry were used to assess the integrity of the external ear...
canal, tympanic membrane, and middle ear space. Pure-tone audiometry was assessed via visual reinforcement audiometry, conditioned play audiometry, or conventional methods, depending on the child’s age, development, cognition, and/or medical status. Pure-tone air-conduction thresholds were measured in dB HL at CFs of 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, and 8.0 kHz. EHF audiometry was evaluated at 9.0, 10.0, 11.2, 12.5, 14.0, and 16.0 kHz in children aged ≥ 5 years (Beahan, Kei, Driscoll, Charles, & Khan, 2012). Pure-tone bone-conduction thresholds were assessed in dB HL at 0.25, 0.5, 1.0, 2.0, 3.0, and 4.0 kHz to establish type of hearing loss (i.e., conductive, sensorineural, or mixed). DPOAEs were measured at the frequency $2f_1-f_2$ at $f_2$ frequencies of 1.5, 2.0, 3.0, 4.0, 6.0, and 8.0 kHz with $L_1 = 65$ dB SPL, $L_2 = 55$ dB SPL, and $f_2/f_1 = 1.22$. SIN testing was administered to English-speaking patients aged ≥ 5 years.

**Instrumentation**

Patients were tested in a double-wall, sound-treated booth meeting ANSI Standard S.31-1999 (American National Standards Institute, 2013). Air-conduction thresholds were obtained using a Grason-Stadler Inc. (GSI) AudioStar Pro or GSI 61 audiometer with Sennheiser HDA 200 or 300 supra-aural headphones. Bone-conduction thresholds were measured with a RadioEar B-71 bone transducer when indicated. Tympanograms were obtained using GSI Tymptast or Tymptstar Pro tympanometers. DPOAEs were assessed with the Otodynamics Otoport Advance system. The Quick Speech-in-Noise (QuickSIN) Test (Etymotic Research, 2001) was administered to patients older than 14 years, and the Bamford–Kowal–Bench Speech-in-Noise (BKB-SIN) Test (Etymotic Research, 2005) was used for patients aged 5–14 years and for adolescents for whom the QuickSIN Test was too difficult.

**Determination of Ototoxicity**

Ototoxicity was assessed using two different criteria. A decline in hearing sensitivity—not clinically significant SNHL per se—for pure-tone thresholds (0.25–16.0 kHz) was defined by the American Speech-Language-Hearing Association (ASHA, 1994) criteria. The ASHA criteria identify a change (i.e., decrease) in hearing sensitivity when compared to baseline measures as follows: (a) ≥ 20 dB HL decrease in pure-tone threshold at a single test frequency, (b) ≥ 10 dB HL decrease in threshold at two adjacent frequencies, or (c) loss of response at three consecutive frequencies where responses were previously obtained. The ASHA criteria are used as a binary outcome (yes or no) measure designed to detect early ototoxic changes before clinical SNHL occurs. The ASHA criteria are valuable in identifying early threshold shifts; however, they are not practical in reporting clinically significant hearing loss in the oncology setting as the criteria are not frequency specific, do not offer any level of severity to ototoxicity change, and require a baseline evaluation for comparison that can be difficult to obtain in medically fragile pediatric patients.

Clinically significant SNHL was determined by assigning an ototoxicity grade based on the Chang Ototoxicity Grading Scale (Chang & Chinosornvatana, 2010; Table 1). The Chang ototoxicity criteria consist of five levels of hearing loss severity, ranging from Grade 0 (no complications) to Grade 4 (severe complications), and utilizes absolute hearing threshold levels highly correlated with recommendations for audiologic intervention (i.e., Chang grades ≥ 2a were significantly associated with the audiologic recommendation for hearing aids and/or frequency modulation systems; Chang & Chinosornvatana, 2010). No distinct grading system has been published for radiation-induced ototoxicity. The Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer published an ear toxicity scoring system that treats the external, middle, and inner ear as one organ without defining frequency-specific criteria (Cox, Stetz, & Pajak, 1995). Although initially developed to assess clinically significant platinum-induced ototoxicity, the Chang Ototoxicity Grading Scale has been used to rate radiation-induced ototoxicity, particularly because it emphasizes SNHL in the higher frequencies (i.e., higher frequencies are more severely affected by radiotherapy) and it includes a criterion (Grade 2b) that captures milder degrees of atypical configurations (i.e., low- or midfrequency) of radiation-induced SNHL (Bass et al., 2016). It should be noted that the Chang Ototoxicity Grading Scale omits grading of SNHL at thresholds of > 15 dB and < 25 dB, thresholds of ≥ 40 dB below 1000 Hz, and thresholds of < 40 dB at 6000 and 8000 Hz, potentially missing patients with minimal hearing loss, moderate to profound low- and midfrequency SNHL, and/or mild high-frequency SNHL. Results from the most recent evaluation were compared to baseline measures to evaluate ototoxicity using both the Chang Ototoxicity Grading Scale and ASHA criteria. For cases of asymmetrical SNHL, the worse ear was used when determining degree of ototoxicity.

A baseline DPOAE response was considered valid when the DPOAE level exceeded the mean level of the noise floor by ≥ 6 dB at each $f_2$ frequency. In addition, at any time point, the following three conditions were met for the DPOAE response to be considered a valid response: (a) normal middle ear function, (b) primary tone-level $L_1$ value of 65 dB SPL ± 2 dB, and (c) primary tone-level $L_2$ value ≤ 40 dB at ≥ 1 kHz.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>≤ 20 dB at 1, 2, and 4 kHz</td>
</tr>
<tr>
<td>1a</td>
<td>≥ 40 dB at 6–12 kHz</td>
</tr>
<tr>
<td>1b</td>
<td>&gt; 20 and &lt; 40 dB at 4 kHz</td>
</tr>
<tr>
<td>2a</td>
<td>≥ 40 dB at ≥ 4 kHz</td>
</tr>
<tr>
<td>2b</td>
<td>&gt; 20 and &lt; 40 dB at &lt; 4 kHz</td>
</tr>
<tr>
<td>3</td>
<td>≥ 40 dB at ≥ 2 kHz</td>
</tr>
<tr>
<td>4</td>
<td>≥ 40 dB at ≥ 1 kHz</td>
</tr>
</tbody>
</table>

*Note.* Sensorineural hearing threshold was assessed by bone conduction or air conduction with normal tympanogram. The worse ear was used when a patient had an asymmetric Chang grade.
of 55 dB SPL ±2 dB. If any of these conditions was not met, the response was excluded from the analysis. No universal criterion for significant change in DPOAE level exists. For this study, the criterion for ototoxic change was defined as a decrease in DPOAE level of ≥ 6 dB at one or more f2 frequencies based on previous work by Bhagat et al. (2010), who utilized a ≥ 6 dB criterion to determine an ototoxic change in DPOAE levels in children treated with carboplatin for retinoblastoma. Comparisons were made between baseline and most recent DPOAE levels.

The critical difference for comparing two conditions provided in the QuickSIN and BKB-SIN test manuals was used to determine a significant clinical change between SIN test scores. To familiarize the patient to the task, one list of five sentences was administered as a practice list at 70 dB HL under headphones in both ears simultaneously. One list pair (i.e., two lists totaling 10 sentences) was then administered, and an average score was calculated according to the scoring guidelines provided in the test manuals. The list pair score was compared to the age-related norms to determine SNR loss. The SNR loss is the increase in SNR required by a listener to obtain 50% of target words correct as compared to performance by age-matched normal hearing listeners. The age-appropriate Wechsler Intelligence Scale was administered at baseline to derive a full-scale IQ (FSIQ), or a working memory index score if FSIQ was unavailable, for each patient. The Wechsler Intelligence Scale for Children–Fourth Edition (Wechsler, 2003) was completed by the majority of patients aged 6–16 years. The normative value of these scores was 100, with a standard deviation of 15. These data were used in this study to describe global cognitive function in patients who completed SIN testing. Patients with an FSIQ score of < 85 were excluded from the SIN analysis.

Statistical Methods

Descriptive statistics were used to summarize patient demographics and clinical characteristics. The McNemar’s exact test was used to compare hearing decline in the EHF range versus the CF range. The Kaplan–Meier curve and estimate were used to describe time to onset of decreased hearing sensitivity. A univariable generalized estimating equation model with repeated measures was used to investigate potential risk factors associated with decreased hearing sensitivity. Potential explanatory variables included age at PRT initiation (years), CRD (cGy [RBE]), gender, and race (White vs. non-White).

For DPOAE data analysis, mixed models for longitudinal data (i.e., random coefficient models) were used. A base model was initially built, including time and ear. For each patient, the first DPOAE test date was counted as Day 1. For each follow-up DPOAE evaluation, the time variable was counted as the days from the first DPOAE date. We started from a full model, which included all covariates of interest: age at PRT initiation, CRD, gender, and race. Then we applied backward elimination, until all variables that remained in the model were significant at the .05 level. This process was repeated for 12 data sets including the right and left ear responses at frequencies 1.5, 2.0, 3.0, 4.0, 6.0, and 8.0 kHz.

A random coefficient model was used to examine SIN performance over time. The definition and derivation of the time variable in this model was equivalent to the one used in the DPOAE analysis. A significance threshold of .05 was used throughout without adjusting for multiplicity. Analyses were performed using SAS 9.4 (SAS Institute) and R 3.3.0 (R Core Development Team; http://www.r-project.org/).

Results

Patient Characteristics

Table 2 provides demographic and clinical characteristics of the 74 evaluable patients. Median age at PRT initiation was 10 years (range, 4–19.3 years), and median CRDs to the left and right ears were 126 cGy (RBE) (range, 0.2–5,449 cGy [RBE]) and 143 cGy (RBE) (range, 0.2–5,215 cGy [RBE]), respectively. Patients received a median of 2 post-PRT evaluations (range, 1–5), with a median follow-up from PRT initiation to latest audiogram of 2 years (range, 0.7–5.2 years).

Ototoxicity Based on the Chang Ototoxicity Grading Scale

No patients had clinically significant SNHL in the CF range. Among the 74 evaluable patients, two (2.7%) had Chang grade > 0 at last evaluation for the EHF range only. One patient received 0.3 and 6.6 cGy (RBE) to the right and left ears, respectively, and had had left ear Chang Grade 1a at frequencies ≥ 10 kHz ranging in severity from moderate to moderately severe. The other patient received 25.8 and 54.2 cGy (RBE) to the right and left ears, respectively, and had bilateral Chang Grade 1a at frequencies ≥ 10 kHz for the right ear and ≥ 9 kHz for the left ear that fell within the moderate severity range.

Ototoxicity Based on the ASHA Criteria

Based on the ASHA criteria at last evaluation, decreased hearing was observed in zero patients for the CF range alone, in nine (12%) patients for the EHF range alone, and in 15 (20%) patients for both the CF and EHF ranges. Patients who met the ASHA criteria for decreased hearing were more likely to experience a decline in the EHF range compared to the CF range (McNemar’s test exact p = .0039; Figure 1). For each patient who met the ASHA criteria, the onset of decreased hearing was defined as the time from PRT initiation to the date when a patient first met the ASHA criteria in either ear. The median time to onset of decreased hearing was 24.6 months (range, 11.1–63.4 months), and the estimated probability of not having decreased hearing sensitivity at the end of 3 years post-PRT was 70% ± 7.4% and 38% ± 15% at 5 years (see Figure 2).
Risk Factors Associated With Hearing Decrease by the ASHA Criteria

Of the 148 ears from 74 evaluable patients, five ears were not included in the analysis due to abnormal middle ear function at either baseline or last audiologic evaluation. Of the remaining 143 ears included in the analysis, 37 ears from 24 patients met the ASHA criteria for decreased hearing sensitivity. In a univariable model, older age at PRT initiation was the only risk factor associated with a decline in hearing sensitivity (see Table 3). The odds ratio for developing a decrease in hearing was estimated to be 1.2 for every 1 year increase in age at PRT initiation (95% confidence interval [1.03, 1.31], \( p = .0114 \)).

DPOAEs

For the analysis of DPOAE measurements, 12 data sets were analyzed based on the combinations of right and left ears at different frequencies: 1.5, 2.0, 3.0, 4.0, 6.0, and 8.0 kHz. The number of patients with valid DPOAE measurements varied from 40 to 69, depending on the test frequency. In all 12 data sets, level reductions were observed at varied rates. DPOAE levels decreased at a much faster rate at higher frequencies (including 6 and 8 kHz) than at lower frequencies, and older age at PRT initiation was associated with decreased levels at 3.0, 4.0, and 6.0 kHz (\( p = .0127 \), \( p = .0283 \), and \( p = .0002 \), respectively; Table 4). Figure 3 illustrates the decrease in mean DPOAE levels.
Figure 2. Kaplan–Meier plot of time-to-onset of decreased hearing by the ASHA criteria. For each of the 24 patients who met the ASHA criteria, the time variable was calculated from the date of proton radiotherapy (PRT) initiation to the date when a patient first met the ASHA criteria in any ear. For each of the 50 patients without decreased hearing, the time variable was calculated from the date of proton radiotherapy initiation to the date of last evaluation.

Discussion

Early changes in auditory function were prospectively and longitudinally evaluated in 74 patients treated with PRT for childhood craniopharyngioma. At last evaluation, no patients experienced clinically significant SNHL in the CF range as defined by the Chang Ototoxicity Grading Scale, and SIN performance did not decline over time. However, almost one third of patients experienced a decrease in hearing sensitivity according to the ASHA criteria in either or both the CF and EHF ranges when compared to baseline measures. Hearing was more likely to decrease in the EHF range compared to the CF range, and DPOAE levels decreased at a faster rate for higher frequencies compared to lower frequencies. Older age at the start of PRT was associated with decreased hearing sensitivity and DPOAE levels.

The first aim of this study was to report the incidence, onset, and severity of ototoxicity by comparing CF and EHF pure-tone audiometric thresholds over time in pediatric patients treated with PRT. Previous studies in children treated with photon-based radiotherapy in the absence of chemotherapy have reported SNHL as an adverse effect. In a study by Williams et al. (2005), radiation-induced SNHL, defined by a 20-dB decrease in hearing from baseline measures at frequencies 250–8000 Hz, was observed in 27% of children. Hua et al. (2008) reported SNHL following cranial radiation in 14% of patients, where SNHL was defined as thresholds greater than 25 dB on at least two consecutive audiologic evaluations with no return to normal hearing on subsequent evaluations. Bass et al. (2016) observed a 14% incidence of SNHL using the Chang Ototoxicity Grading Scale in pediatric patients treated with photon radiation for brain tumors. In the current series, we reported a lower prevalence of SNHL following PRT with only 2.7% (n = 2) of children experiencing a Chang Grade 1a in the EHF range only. Studies on normative thresholds have shown that mean EHF thresholds for school-age children fell below 15 dB HL, comparable to CF thresholds (Anastasio, Radael, Cavalcante, & Hatzopoulos, 2012) and that hearing sensitivity begins to decline in the EHF of 15–18 kHz at approximately 20 years of age (Stelmachowicz, Beauchaine, Kalberer, & Jesteadt, 1989). Thus, age did not contribute to decreased hearing in our study cohort. Although a change in hearing sensitivity using the ASHA criteria was observed in the CF range in 15 patients, all thresholds were < 25 dB, which was not considered to be clinically significant SNHL. Our findings are consistent with other studies that have shown a reduced incidence of SNHL in the CF range in pediatric patients treated with PRT for medulloblastoma (Moeller et al., 2011; Yock et al., 2016) and ependymoma (Macdonald et al., 2013). It should be noted that a limitation of the Chang Ototoxicity Grading Scale, as well as other current ototoxicity scales, is the omission of criteria for minimal hearing loss defined as pure-tone thresholds between 16 and 25 dB HL. Children with minimal SNHL are at risk for academic and psychosocial difficulties (Bess, Dodd-Murphy, & Parker, 1998; Thorpe, Sladen, Murphy, & Boney, 2009) and are

Table 3. Univariable generalized estimating equation model for potential risk factors associated with decreased hearing sensitivity.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at PRT (years)</td>
<td>1.165</td>
<td>[1.035, 1.311]</td>
<td>.0114</td>
</tr>
<tr>
<td>Race (White)</td>
<td>0.918</td>
<td>[0.337, 2.50]</td>
<td>.8674</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>0.689</td>
<td>[0.266, 1.787]</td>
<td>.4441</td>
</tr>
<tr>
<td>CRD (cGy [RBE])</td>
<td>0.990</td>
<td>[0.935, 1.047]</td>
<td>.7146</td>
</tr>
</tbody>
</table>

Note. OR = odds ratio; CI = confidence interval; PRT = proton radiotherapy; CRD = cochlear radiation dose; cGy (RBE) = centigray (relative biological effectiveness).
Table 4. Mixed-model analyses of distortion product otoacoustic emission level over time.

<table>
<thead>
<tr>
<th>Frequency (kHz)</th>
<th>No. of patients</th>
<th>%&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Effect</th>
<th>Estimate</th>
<th>95% CI of the estimate</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>67</td>
<td>91</td>
<td>Time (years)</td>
<td>-0.7009</td>
<td>[-1.1636, -0.2382]</td>
<td>.0035</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>93</td>
<td>Time (years)</td>
<td>-0.8780</td>
<td>[-1.2476, -0.5044]</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>89</td>
<td>Time (years)</td>
<td>-0.7789</td>
<td>[-1.1568, -0.4010]</td>
<td>.0001</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>85</td>
<td>Age at PRT initiation (years)</td>
<td>-0.4053</td>
<td>[-0.7208, -0.0898]</td>
<td>.0127</td>
</tr>
<tr>
<td>6</td>
<td>59</td>
<td>80</td>
<td>Age at PRT initiation (years)</td>
<td>-0.4080</td>
<td>[-0.7712, -0.0448]</td>
<td>.0283</td>
</tr>
<tr>
<td>8</td>
<td>40</td>
<td>54</td>
<td>Age at PRT initiation (years)</td>
<td>-0.7223</td>
<td>[-1.0931, -0.3515]</td>
<td>.0002</td>
</tr>
</tbody>
</table>

Note. CI = confidence interval; PRT = proton radiotherapy.

<sup>a</sup>Percentage was calculated using 74 evaluable patients.

currently not identified using the Chang Ototoxicity Grading Scale or other ototoxicity criteria.

One explanation for the lower prevalence of radiation-induced SNHL observed in our study sample is overall lower radiation exposure to the cochlea, which may be attributed to the use of PRT. The median CRD for our sample was 126 and 143 cGy (RBE) for the left and right ears, respectively, compared to higher CRDs reported in previous studies, for example, a median CRD of 29.5 Gy for the left ear and 28.8 Gy for the right ear (Bass et al., 2016), a mean CRD of 34.8 Gy between ears (Hua et al., 2008), and a median CRD of 54 Gy between ears (Williams et al., 2005). These studies have also demonstrated that patients exposed to higher CRDs are more likely to develop SNHL. In our study, CRD was not associated with decreased hearing sensitivity (p = .7146); however, most of the patients in our cohort received low CRDs (i.e., less than 2,000 cGy [RBE] as seen in Table 6), limiting our analysis of a potential dose effect.

The median time to onset of decreased hearing per the ASHA criteria in our series occurred at 24.6 months post-PRT, sooner than the median time to onset of SNHL at 43.2 months (Bass et al., 2016) and the mean time to onset of 49 months (Hua et al., 2008) previously reported in children treated with photon-based radiotherapy. The earlier time to onset of decreased hearing observed in our study is likely due to the use of the ASHA criteria, criteria that are used to measure a change in hearing sensitivity and not clinically significant SNHL. In addition, we measured EHF thresholds, which are likely to decline sooner than CF thresholds. Previous studies reported absolute hearing threshold outcomes in the CF range only; changes in hearing sensitivity from baseline measures for CF and EHF thresholds were not measured in previous reports. We hypothesized that hearing thresholds would decline first and more severely in the EHF range compared to hearing thresholds in the CF range. Our findings supported our hypothesis that decreased hearing sensitivity occurs sooner and more severely in the EHF range than the CF range. Other studies have drawn similar conclusions in patients undergoing ototoxicity monitoring for cisplatin chemotherapy (Fausti et al., 1994; Knight et al., 2007). Longer audiologic follow-up in our study cohort is needed to determine if changes in the EHF range predict subsequent CF SNHL.

The second aim of this study was to examine change in DPOAE levels acquired before and after PRT. We hypothesized that DPOAEs would reveal cochlear hair cell damage before SNHL appeared in the CF range. Studies have demonstrated that DPOAEs exhibit subtle cochlear OHC damage prior to hearing threshold shifts in the CF range (Bhagat et al., 2010; Knight et al., 2007; Littman et al., 1998; Lonsbury-Martin & Martin, 2001). Likewise, patients in our study who experienced a decline in DPOAE levels did not exhibit clinically significant SNHL in the CF range, implying that DPOAEs can also detect subtle cochlear damage before SNHL is identified in the CF range in children treated with PRT. In addition, our findings revealed that reductions in DPOAE levels occurred at a much faster rate in the higher frequencies compared to the lower frequencies. This is not surprising as other studies have demonstrated that radiation-induced SNHL is more severe in the higher frequencies (Bass et al., 2016; Fong et al., 1995; Hua et al., 2008; Williams et al., 2005). Studies in children treated with
platinum chemotherapy have also found that DPOAE level reductions are greater for the higher frequencies than the lower frequencies (Bhagat et al., 2010; Knight et al., 2007). Whether or not clinically significant SNHL will eventually develop in our study patients remains unclear at this time; thus, long-term audiologic follow-up in patients who receive PRT is warranted.

The third aim of this study was to explore the potential impact PRT had on SIN perception. We hypothesized that SIN perception would decline from baseline measures; however, in the current study, we did not observe a significant decline in SIN perception over time among patients who were administered the BKB-SIN Test. One study demonstrated that patients with cisplatin-induced SNHL had poorer than expected perception of speech in the presence of background noise (Einarsson et al., 2011); however, this is not surprising given the severe loss of high-frequency hearing typically observed in patients treated with cisplatin. Although some patients in our study experienced a decline in hearing sensitivity from baseline to last evaluation, all patients’ hearing remained within the normal hearing range for the CFs—the frequencies most important for speech perception.

An exploratory aim of this study was to identify risk factors, including age at PRT initiation (years), CRD (cGy [RBE]), gender, and race (White vs. non-White), that may be associated with decreased auditory function. Age at initiation of PRT was the only variable that was significantly associated with decreased auditory function in our cohort. The association between age at initiation of conventional radiotherapy and the development of SNHL was previously reported in a study by Bass et al. (2016) that showed children younger than 3 years were twice as likely to develop SNHL compared to older children. Conversely, data from this study revealed that older children at initiation of PRT were 1.2 times more likely to experience decreased hearing sensitivity. In addition, older age at PRT initiation was also associated with reductions in DPOAE levels for the higher frequencies 3, 4, and 6 kHz. The difference in age for the participants evaluated between these two studies may explain the discrepancy in the findings, given that children younger than 4 years were not included in the current study analysis, as reliable responses for threshold CF and EHF audiometry, DPOAEs, and SIN testing could not be obtained for very young children. Also, the measurements and criteria used to define ototoxicity differed across studies, potentially impacting the association between age and SNHL.

The strengths of this research include prospective and comprehensive audiologic evaluations and homogenous

### Table 5. Number of ears that met criterion reduction for decreased distortion product otoacoustic emission level.

<table>
<thead>
<tr>
<th>Frequency (kHz)</th>
<th>No. of eligible right ears</th>
<th>No. of right ear ≥ 6 dB reduction</th>
<th>%</th>
<th>No. of eligible left ears</th>
<th>No. of left ear ≥ 6 dB reduction</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>60</td>
<td>11</td>
<td>18.3</td>
<td>60</td>
<td>11</td>
<td>18.3</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>11</td>
<td>17.2</td>
<td>59</td>
<td>10</td>
<td>16.9</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>18</td>
<td>27.7</td>
<td>59</td>
<td>16</td>
<td>27.1</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>18</td>
<td>27.7</td>
<td>64</td>
<td>18</td>
<td>28.1</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>20</td>
<td>30.8</td>
<td>63</td>
<td>29</td>
<td>46</td>
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<tr>
<td>8</td>
<td>35</td>
<td>14</td>
<td>40</td>
<td>31</td>
<td>14</td>
<td>45.2</td>
</tr>
</tbody>
</table>

### Table 6. Number of patients who did or did not meet the ASHA criteria for decreased hearing at last evaluation according to CRD.

<table>
<thead>
<tr>
<th>CRD (cGy [RBE])a</th>
<th>Met the ASHA criteria for decreased hearing at last evaluation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
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<tr>
<td>0–25</td>
<td>13</td>
<td>61.9</td>
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<tr>
<td>25–50</td>
<td>2</td>
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<td>50–75</td>
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<td>40.0</td>
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<tr>
<td>75–100</td>
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<td>50.0</td>
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<td>100–1,000</td>
<td>18</td>
<td>81.8</td>
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<tr>
<td>1,000–2,000</td>
<td>9</td>
<td>81.8</td>
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<tr>
<td>2,000–3,000</td>
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<tr>
<td>3,000–4,000</td>
<td>2</td>
<td>66.7</td>
</tr>
<tr>
<td>4,000–5,000</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>5,000–6,000</td>
<td>1</td>
<td>50.0</td>
</tr>
</tbody>
</table>

Note. ASHA = American Speech-Language-Hearing Association; CRD = cochlear radiation dose; cGy (RBE) = centigray (relative biological effectiveness).

aHigher cochlear dose that a patient received between the left and right ears.
radiation exposure. Our findings, however, should be considered with caution in light of study limitations. Only patients with sufficient audiologic baseline and follow-up data were included in the analysis; thus, auditory function in patients without adequate audiologic data may have differed from that of study participants. In addition, follow-up time varied from 0.7 to 5.2 years with median follow-up time of 2 years, potentially missing late onset changes in auditory function in patients with short follow-up time.

In summary, early auditory outcomes were favorable in patients treated with PRT. Preservation of hearing within the CF frequency range critical for speech acquisition and comprehension was maintained with no decline in SIN performance. However, subtle decreases in hearing sensitivity, particularly in the EHF range, and DPOAE levels were observed. Long-term audiologic follow-up is warranted to determine if decreased hearing sensitivity in the EHF range and decreased DPOAEs predict subsequent CF SNHL in patients treated with PRT.

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References


