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SURVIVORSHIP: RESEARCH ARTICLE

Severity of hearing loss after platinum chemotherapy in childhood cancer survivors

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Abstract

Background: Hearing loss is a potential side effect from childhood cancer treatment. We described the severity of hearing loss assessed by audiometry in a representative national cohort of childhood cancer survivors (CCS) and identified clinical risk factors.

Procedure: We included all CCS from the Swiss Childhood Cancer Registry who were diagnosed ≤18 age and treated with platinum-based chemotherapy between 1990 and 2014. We extracted audiograms, treatment-related information, and demographic data from medical records. Two reviewers independently assessed the severity of hearing loss at latest follow-up using the Münster Ototoxicity Scale. We used ordered logistic regression to identify clinical risk factors for severity of hearing loss.

Results: We analyzed data from 270 CCS. Median time from cancer diagnosis to last audiogram was 5 years (interquartile range 2.5–8.1 years). We found 53 (20%) CCS with mild, 78 (29%) with moderate, and 75 (28%) with severe hearing loss. Higher

Abbreviations: BC, bone conduction; CCS, childhood cancer survivors; CI, confidence interval; CNS, central nervous system; CRT, cranial radiation therapy; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; OR, odds ratio; SCCR, Swiss Childhood Cancer Registry; SIOP, International Society of Pediatric Oncology.

severity grades were associated with (a) younger age at cancer diagnosis (odds ratio [OR] 5.4, 95% confidence interval [CI]: 2.5–12.0 for <5 years); (b) treatment in earlier years (OR 4.8, 95% CI: 2.1–11.0 for 1990–1995); (c) higher cumulative cisplatin doses (OR 13.5, 95% CI: 4.7–38.8 for >450 mg/m^2); (d) concomitant cranial radiation therapy (CRT) (OR 4.4, 95% CI: 2.5–7.8); and (e) hematopoietic stem cell transplantation (HSCT) (OR 2.7, 95% CI: 1.0–7.2).

Conclusion: Three of four CCS treated with platinum-based chemotherapy experienced some degree of hearing loss. We recommend closely monitoring patient's hearing function if treated at a young age with high cumulative cisplatin doses, and concomitant CRT as part of long-term care.

KEYWORDS
cancer registry, childhood cancer survivors, cranial radiation, ototoxicity, platinum compounds

1 | INTRODUCTION

Hearing loss is a side effect of ototoxic treatments in childhood cancer survivors (CCS).[1,2] Platinum compounds are highly effective in solid tumors, but their use in pediatric patients is limited because of ototoxicity. Cisplatin—and to a lesser extent, carboplatin—can damage hair cells of the cochlea, the stria vascularis, and the spiral ganglion neurons, resulting in sensorineural hearing loss.[1–3] Hearing loss induced by platinum compounds is usually permanent, binaural, and primarily affects higher frequencies of the auditory spectrum.[1,3,4] Even though hearing loss is not life-threatening, it may impair speech development, academic performance, and quality of life.[5–7]

Research on hearing loss after platinum-based chemotherapy among CCS is extensive; however, evidence from representative nationwide samples is limited.[8] Previous studies were often single-center[9–16] or included selected clinics.[17–23] Most studies had relatively small samples,[10,12,14] were restricted to specific diagnostic groups,[11,15,17,19,23] or had short follow-up time.[20,21] These limitations resulted in selective samples with limited generalizability to the overall population of CCS treated with platinum-based chemotherapy. Also, there was no consensus on the definition of hearing loss across studies, and hearing loss was often reported as a binary outcome with an artificial cutoff that differed between studies. We overcame these limitations by using detailed treatment and audiogram data, which allowed description of different levels of hearing loss severity, among a representative national cohort of CCS. We also quantified the influence of clinical risk factors on the severity of hearing loss.

2 | METHODS

2.1 | Study population

The study population included CCS registered in the Swiss Childhood Cancer Registry (SCCR) who had been diagnosed before age 19 and treated with platinum-based chemotherapy in a specialized pediatric oncology clinic between 1990 and 2014 in Switzerland. The SCCR is a national, population-based registry in Switzerland; it includes all people diagnosed with leukemia, lymphoma, central nervous system (CNS) tumor, malignant solid tumor, or Langerhans cell histiocytosis before age 21 since 1976.[24] For inclusion in our study, patients had to have normal hearing before starting cancer treatment and an available post-treatment audiogram. We excluded all who were not alive during data collection in 2015; we assumed children's hearing testing in palliative settings was not a priority. In addition, their medical records are often difficult to access or not available for research purposes.[25] Ethical approval for the SCCR was granted along with the nationwide Swiss Childhood Cancer Survivor Study[26] by the Ethics Committee of the Canton of Bern (KEK-BE: 166/2014; 2021-01462). We also contributed data from our study population to the European PanCareLIFE project.[27]

2.2 | Study procedure

We identified eligible CCS using information on vital status and treatment from the SCCR in September 2015. Exact treatment information about type and dose of chemotherapy is not available in the SCCR. Therefore, we identified CCS who had been treated with platinum compounds using an intention-to-treat approach based on the treatment protocol. We then collected audiograms and extracted treatment information about platinum-based chemotherapy and cranial radiation of eligible CCS from medical records in ear, nose, and throat departments and pediatric oncology departments of all specialized pediatric oncology clinics in Switzerland.[28] We extracted demographic and cancer-related information from the SCCR, including sex, cancer diagnosis according to the International Classification of Childhood Cancer (3rd edition[29]), year of cancer diagnosis, age at cancer diagnosis, and history of hematopoietic stem cell transplantation (HSCT; yes/no).

TABLE 1 Criteria of the Münster and SIOP Boston Ototoxicity Scale for hearing loss following platinum-based chemotherapy

Münster Ototoxicity Scale[30]		SIOP Boston Ototoxicity Scale[32]	
Grade	Measured hearing loss	Grade	Measured hearing loss
0	≤10 dB in all frequencies	0	≤20 dB at all frequencies
1	15–20 dB in at least one frequency or tinnitus	1	Above 4 kHz >20 dB
2	Hearing losses of more than 20 dB in the high-frequency range (from 4 kHz and above)	2	At 4 kHz and above >20 dB
2a	>20 to ≤40 dB		
2b	>40 to ≤60 dB		
2c	>60 dB		
3	Hearing losses of more than 20 dB in the low-frequency range (below 4 kHz)	3	At 2 kHz or 3 kHz and above >20 dB
3a	>20 to ≤40 dB		
3b	>40 to ≤60 dB		
3c	>60 dB		
4	Averaged hearing loss below 4 kHz of at least 80 dB, averaged from 500 Hz, 1 kHz, and 2 kHz	4	At 2 kHz and above >40 dB

Abbreviations: dB, decibel; (k)Hz, (kilo)Hertz.

2.3 | Assessment of hearing

The main outcome for our study was hearing function assessed by ear-specific pure-tone audiometry, then classified according to the Münster Ototoxicity Scale.[30] We searched through medical records of eligible CCS in clinics and collected audiological evaluations and corresponding audiology reports.[28] Collected hearing evaluations included pure-tone audiometry, free-field audiometry, auditory brainstem response, otoacoustic emissions testing, speech audiometry, and tympanometry. Hearing loss before start of platinum-based chemotherapy was determined either with pure-tone audiometry or by a medical report of another baseline hearing evaluation. Where no baseline hearing evaluation was available and nothing was noted in the medical records, we assumed, based on estimates for a normal pediatric population in high-income countries,[31] that hearing function was within normal range.

We used the most recent pure-tone audiogram after completion of platinum-based chemotherapy for this analysis. Each audiogram was graded according to the Münster Ototoxicity Scale by two trained independent reviewers (Table 1).[30] Discrepancies in grading were resolved by discussion or by judgment of a senior audiologist (Antoinette am Zehnhoff-Dinnesen, Ross Parfitt). Where a significant difference between air conduction and bone conduction (AC/BC) indicated a potential conductive hearing loss, we used BC thresholds for classification. If there was uncertainty, we also looked at the tympanogram (if available) or the corresponding audiological report. For validation, we additionally applied the classification system of the International Society of Pediatric Oncology (SIOP) Boston Ototoxicity Scale.[32] The Münster and the SIOP Boston Ototoxicity Scales were developed for the scientific assessment of ototoxicity following platinum-based chemotherapy; both have high sensitivity and specificity compared to other grading scales.[23,30,33,34] When the grading differed between the right and the left ears, we used the more affected ear to assign severity of hearing loss. We categorized severity into (a) no (Münster grade 0); (b) mild (Münster grade 1); (c) moderate (Münster grades 2a–2c); or (d) severe hearing loss (Münster ≥grade 3).[30] Previous studies using the Münster Ototoxicity Scale for audiological classification, defined clinically relevant hearing loss as Münster grade ≥2b.[8,35] Applying the criteria of the SIOP Boston Ototoxicity Scale, we categorized severity of hearing loss accordingly into (a) no (SIOP Boston grade 0); (b) mild (SIOP Boston grade 1); (c) moderate (SIOP Boston grade 2); or (d) severe hearing loss (SIOP Boston ≥grade 3). We defined clinically relevant hearing loss as SIOP Boston grade ≥2.[18]

2.4 | Assessment of ototoxic treatments and other potential risk factors

Ototoxic treatment with platinum-based chemotherapy and cranial radiation therapy (CRT) was our main exposure of interest. We extracted the treatment protocol, treatment arm, type of prescribed platinum agent with total dose per cycle (mg/m^2), and CRT (yes/no) from medical records.[28] We calculated the total cumulative dose (mg/m^2) of administered cisplatin and carboplatin separately. We divided total cumulative cisplatin dose (mg/m^2) into four categories: (a) no cisplatin; (b) ≤300 mg/m^2; (c) 301–450 mg/m^2; and (d) >450 mg/m^2. We similarly categorized total cumulative carboplatin dose (mg/m^2) into four categories: (a) no carboplatin; (b) <1500 mg/m^2; (c) 1500–3000 mg/m^2; and (d) >3000 mg/m^2. Both categorizations were based on previous studies.[8,35] Other exposures that may increase the risk for hearing loss or modify the risk of ototoxic treatments were age at cancer diagnosis,[8,18,21] year of cancer diagnosis[2] as a proxy for changing treatment regimens, and HSCT.[36] We separated age at cancer diagnosis into three categories (<5, 5–9, and ≥10 years)[18,21] and divided

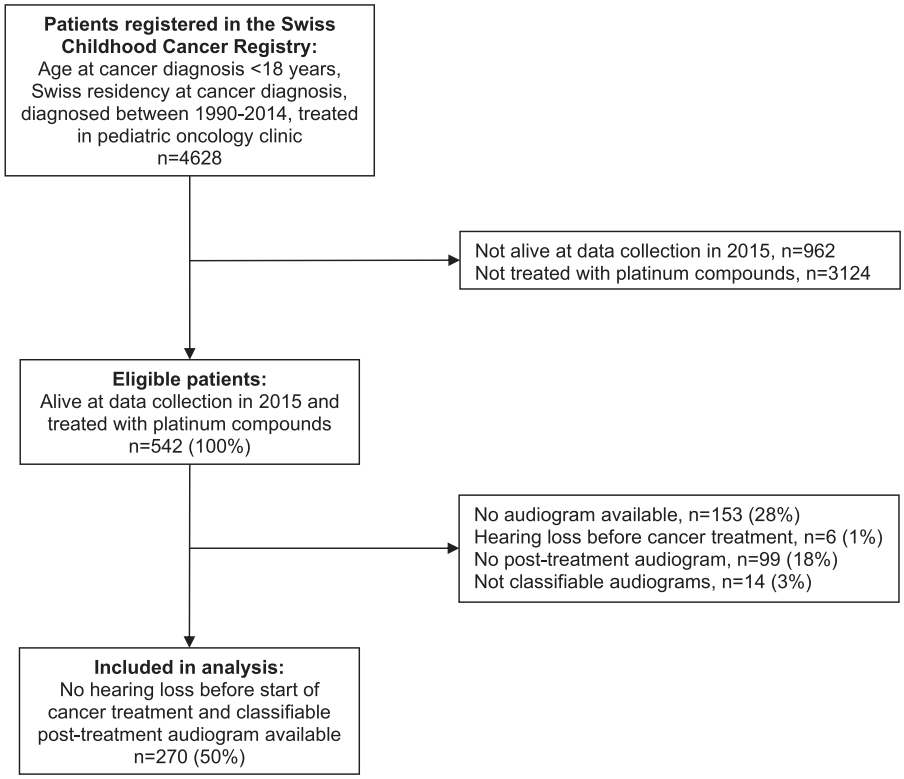

FIGURE 1 Flowchart of study population

year of cancer diagnosis into four periods (1990–1995, 1996–2001, 2002–2007, and 2008–2014).

2.5 | Statistical analysis

First, we described the severity of hearing loss overall and stratified by period of cancer diagnosis, age at cancer diagnosis, and type of cancer diagnosis. We performed Cuzick's test for trend to assess differences across periods of cancer diagnosis and age at cancer diagnosis categories. We used chi-square statistics to compare CCS diagnosed with a CNS tumor or neuroblastoma with CCS diagnosed with a malignant bone tumor. To estimate potential effects of selection bias on results, we re-estimated prevalence of hearing loss in a best-case scenario, which assumed that all CCS without post-treatment audiograms in their medical records, who were excluded from the analysis, had normal hearing.

Second, we fitted univariable and multivariable ordered logistic regression models to identify demographic and clinical factors associated with severity of hearing loss. We included sex, age at most recent audiogram, age at cancer diagnosis, period of cancer diagnosis, cumulative dose of cisplatin and carboplatin, concomitant CRT (yes/no), and HSCT (yes/no) as explanatory variables in the univariable regression models. Variables associated with the severity of hearing loss at $p < .05$ in the univariable analyses were included in the multivariable ordered logistic regression model. We a priori decided to include age at most recent audiogram (<10, 10–15, and >15 years), age at cancer diagnosis, and sex in the multivariable analysis independent of the strength of the association in the univariable analysis.[3,8] To account for potential linear relationships between explanatory variables and the severity of hearing loss, we also performed a sensitivity analysis including age at most recent audiogram, age at cancer diagnosis, year of cancer diagnosis, and cumulative doses of cisplatin and carboplatin as continuous variables in our regression model. We further replicated our multivariable model in a validation analysis using the SIOP Boston Ototoxicity Scale. We calculated global *p*-values using likelihood-ratio tests (LRT).

We used Stata version 15.1 (StataCorp LP, Austin, TX, USA) for all analyses.

3 | RESULTS

3.1 | Characteristics of study population

Among 4628 children and adolescents diagnosed with cancer between 1990 and 2014 in Switzerland, 542 were treated with platinum-based chemotherapy and alive at the time of data collection in 2015 (Figure 1). Of those eligible for the study, 153 (28%) had no available audiogram in their medical records, six (1%) had evidence of hearing loss before starting cancer treatment, 99 (18%) had no post-treatment audiogram, and 14 (3%) had only audiograms available that were nonclassifiable. We included a total of 270 (50%) CCS in the analysis.

The sample for analysis included 116 (43%) females and 154 (57%) males, with a median age at most recent audiogram of 13.5 years (interquartile range [IQR]: 9.3–17.0 years) and a median age at cancer diagnosis of 6.8 years (IQR: 2.1–11.7 years) (Table 2). Common cancer diagnoses were CNS tumors (n = 104; 39%), malignant bone tumors (n = 62; 23%), and neuroblastomas (n = 39; 14%). Over half (n = 154; 57%) had been treated with cisplatin, 62 (23%) with carboplatin, and 54 (20%) with both platinum compounds. Of those who had received cisplatin, the median cumulative dose was 400 mg/m^2 (IQR: 314–480 mg/m^2). Of those who received carboplatin, the median cumulative dose was 2135 mg/m^2 (IQR: 1460–3200 mg/m^2). Concomitant CRT was administered in 36% (n = 98), and 10% (n = 26) had undergone HSCT. Median time from cancer diagnosis to most recent audiogram was 5 years (IQR: 2.5–8.1 years) Table 2.

Eligible CCS who were included in our analysis differed significantly from those who were excluded in terms of sex, period and type of cancer diagnosis, platinum agent received, and CRT (Table 1). Included CCS were more often males (p = .025) diagnosed with malignant bone tumors, CNS tumors, neuroblastoma, or hepatic tumors (p < .001) who had more often received cisplatin (p < .001) or CRT (p < .001).

3.2 | Prevalence and severity of hearing loss after platinum chemotherapy

Among three out of four CCS, the most recent audiogram showed evidence for some degree of hearing loss (n = 206; 76%, 95% confidence interval [CI]: 71%–81%; Münster grade ≥1). We found 53 (20%, 95% CI: 15%–25%) CCS with mild (Münster grade 1), 78 (29%, 95% CI: 24%–35%) with moderate (Münster grades 2a–2c), and 75 (28%, 95% CI: 23%–34%) with severe hearing loss (Münster grade ≥3). We identified 134 (50%, 95% CI: 44%–56%) CCS with clinically relevant hearing loss (Münster grade ≥2b). In a sensitivity analysis, in cases when we found no classifiable ear-specific pure-tone audiogram after treatment in their medical records (n = 266), we assumed that all of them had normal hearing. Under this best-case scenario, prevalence for any degree of hearing loss in the study population would be 38% (95% CI: 34%–43%; Münster grade ≥1) and prevalence of severe hearing loss would be 14% (95% CI: 11%–17%; Münster grade ≥3).

The prevalence of mild, moderate, and severe hearing loss differed by period of cancer diagnosis (p-trend <.001), age at cancer diagnosis (p-trend = .004), and type of cancer diagnosis (Figure 2; Table S1). Prevalence of severe hearing loss (Münster grade ≥3) decreased from 50% among CCS diagnosed between 1990 and 1995 to 12% among CCS diagnosed between 2008 and 2014. We also observed a higher prevalence of severe hearing loss among CCS diagnosed with neuroblastoma (p <.001) and CNS tumors (p = .001) compared to CCS diagnosed with malignant bone tumors.

Using the SIOP Boston Ototoxicity Scale, we identified 152 CCS (56%, 95% CI: 50%–62%) with some degree of hearing loss (SIOP Boston grade ≥1). We found 54 (20%, 95% CI: 15%–25%) CCS with mild (SIOP Boston grade 1), 23 (9%, 95% CI: 5%–13%) with moderate (SIOP Boston grade 2), and 75 (28%, 95% CI: 23%–34%) with severe hearing loss (SIOP Boston grade ≥3). The frequency of clinically relevant hearing loss was 36% (n = 98; 95% CI: 31%–42%; SIOP Boston grade ≥2).

3.3 | Clinical factors associated with the severity of hearing loss

Our multivariable analysis suggested CCS (a) over age 15 at their most recent audiogram (odds ratio [OR] 3.0, 95% CI: 1.3–7.0 for >15 years) and (b) under age 5 at cancer diagnosis (OR 5.4, 95% CI: 2.5–12.0 for <5 years) who received (c) treatment in earlier decades (OR 4.8, 95% CI: 2.1–11.0 for 1990–1995), (d) higher cumulative doses of cisplatin (OR 13.5, 95% CI: 4.7–38.8 for >450 mg/m^2), (e) concomitant CRT (OR 4.4, 95% CI: 2.5–7.8), or (f) HSCT (OR: 2.7, 95% CI: 1.0–7.2) were associated with higher severity grades of hearing loss (Table 3). If a CCS received concomitant CRT, then the odds of a worse hearing by one category (i.e., severe instead of moderate, moderate instead of mild, or mild instead of normal) were four times greater. Results were similar when we included age at most recent audiogram, age at cancer diagnosis, year of cancer diagnosis, and cumulative doses of cisplatin and carboplatin as continuous instead of categorical variables (Table S2). Sex and cumulative doses of carboplatin were not significantly associated in the multivariable analysis. We observed similar associations using the SIOP Boston Ototoxicity Scale (Figure 3, Table S3).

4 | DISCUSSION

Our nationwide study showed that three of four CCS treated with platinum chemotherapy experienced some degree of hearing loss at latest follow-up. One of four CCS suffered from severe hearing loss, indicating a potential need for hearing aids. We observed the highest prevalence of mild, moderate, and severe hearing loss among CCS diagnosed with CNS tumors and neuroblastoma. Higher severity was associated with younger age at cancer diagnosis, treatment in earlier years, higher cumulative dose of cisplatin, and concomitant CRT.

Our study is strengthened by reporting on different degrees of hearing loss after platinum-based chemotherapy in a representative national cohort of CCS diagnosed over a period of more than 20 years. We used detailed treatment and audiogram data from medical records. Audiograms were assessed by two trained independent reviewers who were blinded to demographic and clinical variables. We used two established and standardized ototoxicity grading scales developed for a pediatric population. CCS with hearing loss before cancer treatment were excluded from our analysis. However, our study findings may be affected by the lack of a standardized follow-up program for ototoxicity surveillance and variability in testing between clinics and physicians. CCS at particular risk for ototoxicity have been more likely to be included in our study, leading to an overestimation of the prevalence of hearing loss.[28] We estimated the effect that this bias might have had on the results in a best-case scenario; we assumed that all CCS with missing audiograms who were eligible but excluded from our

TABLE 2 Demographic and clinical characteristics of study population

	Eligible population included in the study ($n = 270$)		Eligible population not included in the study[a] ($n = 272$)		
Demographic characteristics	***n***	**(%)**	***n***	**(%)**	***p*-Value[b]**
Sex					**.025**
Male	154	(57)	129	(47)	
Female	116	(43)	143	(53	
Age at most recent audiogram					n.a.[c]
<10 years	81	(30)	–	–	
10–15 years	108	(40)	–	–	
>15 years	81	(30)	–	–	
Clinical characteristics					
Age at cancer diagnosis					.065
<5 years	112	(41)	140	(51)	
5–9 years	67	(25)	57	(21)	
10–18 years	91	(34)	75	(28)	
Period of cancer diagnosis					**.047**
1990–1995	48	(18)	39	(14)	
1996–2001	75	(28)	84	(31)	
2002–2007	82	(30)	61	(22)	
2008–2014	65	(24)	88	(32)	
Diagnosis (ICCC-3)					**<.001**
III CNS and miscellaneous intracranial and intraspinal neoplasms	104	(39)	89	(33)	
IV Neuroblastoma and other peripheral nervous cell tumors	39	(14)	31	(11)	
V Retinoblastoma	5	(2)	40	(15)	
VI Renal tumors	6	(2)	16	(6)	
VII Hepatic tumors	15	(6)	7	(3)	
VIII Malignant Bone tumors	62	(23)	29	(11)	
IX Soft tissue and other extraosseous sarcoma	12	(4)	25	(9)	
X Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	27	(10)	33	(12)	
XII Other and unspecified malignant neoplasms	–	–	2	(1)	
Treatments[d]					
Platinum agent					**<.001**
Cisplatin	154	(57)	73	(27)	
Carboplatin	62	(23)	143	(53)	
Cisplatin and carboplatin	54	(20)	46	(17)	
Missing	–	–	10	(4)	
Cumulative cisplatin dose categories					n.a.[c]
No cisplatin	62	(23)	–	–	
≤300 mg/m^2	51	(19)	–	–	
301–450 mg/m^2	71	(26)	–	–	
>450 mg/m^2	86	(32)	–	–	

(Continues)

TABLE 2 (Continued)

Demographic characteristics	Eligible population included in the study ($n = 270$)		Eligible population not included in the study[a] ($n = 272$)		
	n	(%)	*n*	(%)	*p*-Value[b]
Cumulative carboplatin dose categories					n.a.[c]
No carboplatin	154	(57)	–	–	
<1500 mg/m^2	29	(11)	–	–	
1500–3000 mg/m^2	53	(20)	–	–	
>3000 mg/m^2	32	(12)	–	–	
Missing	2	(1)	–	–	
Cranial radiation					**<.001**
No	172	(64)	217	(80)	
Yes	98	(36)	55	(20)	
HSCT					.469
No	244	(90)	246	(90)	
Yes	26	(10)	21	(8)	
Missing	–	–	5	(2)	
Time between diagnosis and most recent audiogram					n.a.[c]
<5 years	135	(50)	–	–	
5–10 years	90	(33)	–	–	
>10 years	45	(17)	–	–	

Abbreviations: CNS, central nervous system; HSCT, hematopoietic stem cell transplantation; ICCC-3, International Classification of Childhood Cancer, 3rd edition; IQR, interquartile range; n.a., not applicable.

[a]Reasons for exclusion: no audiogram available ($n = 153$; 28%); hearing loss before cancer treatment ($n = 6$; 1%); no post-treatment audiogram ($n = 99$; 18%); not classifiable audiograms ($n = 14$; 3%).

[b]*p*-Values calculated from chi-square statistics comparing included to excluded childhood cancer survivors.

[c]Age at most recent audiogram, cumulative doses of cisplatin, cumulative doses of carboplatin, and time between diagnosis and most recent audiogram are not available for excluded childhood cancer survivors.

[d]Each subject could have had more than one treatment modality.

analysis had normal hearing. Under this (very optimistic) assumption, the prevalence for any degree of hearing loss in the population would still be 38%, and for severe hearing loss it would be 14%. Other limitations include the retrospective study design, lack of data about other ototoxic drugs, such as aminoglycoside antibiotics or otoprotective drugs.[8,37] However, exposure to otoprotective drugs is unlikely as no such drug has been approved in Switzerland so far. Furthermore, we only included CCS in our study who had been exposed to platinum-based chemotherapy and who were alive at the time of data extraction, which limits generalizability to the overall population of CCS.[38]

There is wide variability in reported prevalence and severity of hearing loss among CCS. A recent review reported a wide range of prevalence estimates—from 2% to 90%—of platinum-induced hearing loss.[39] Comparability across studies is limited by varying definitions of hearing loss, inclusion criteria, assessment of ototoxic treatments, and observation periods.[39] The review did not include two recent studies from the Netherlands[8] and North America[18] with much larger sample sizes. Clemens and colleagues identified 42% of CCS with hearing loss defined as Münster grade ≥2b.[8] This is comparable to our findings for Münster grade ≥2b with 50% of CCS with hearing loss. The slightly higher prevalence in our study may be explained by the inclusion of CCS with concomitant CRT.[8] The North American study by Moke and colleagues, which included children, adolescents, and young adults with concomitant CRT, found a prevalence of 39% with SIOP Boston[32] grade ≥2 by end of treatment and 44% at latest follow-up, which is consistent with our study.[18] Differences in prevalence estimates between the Münster and SIOP Boston Ototoxicity Scales may be attributed to the higher sensitivity of the Münster Ototoxicity Scale, which is specifically designed for early detection of hearing loss.[30,33,40] We also found that CCS diagnosed with neuroblastoma and CNS tumors had the highest prevalence of mild, moderate, and severe hearing loss. This is consistent with previous studies.[2,18,19] Patients with CNS tumors are exposed to additional risk factors for hearing loss, such as the neurotoxic vinca-alkaloid vincristine,[18,41,42] cerebrospinal fluid-shunt implants,[43] and brain surgery involving the auditory system.[1] Patients with neuroblastomas are often treated with high doses of cisplatin in combination with myeloablative doses of carboplatin.[18,19] These intensive, multiagent chemotherapies increase the risk for complications, such as febrile neutropenia and serious bacterial infections, which may require treatment with aminoglycoside antibiotics.[19,44]

TABLE 3 Clinical risk factors associated with the severity of hearing loss from univariable and multivariable ordered[a] logistic regression[b]

	No hearing loss (Münster grade 0) $n = 64$		Mild hearing loss (Münster grade 1) $n = 53$		Moderate hearing loss (Münster grade 2) $n = 78$		Severe hearing loss (Münster grades 3 and 4) $n = 75$		Univariable		Multivariable	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	OR[c] (95% CI)	*p*-Value[d]	OR[c] (95% CI)	*p*-Value[d]
Sex										.435		.722
Female	31	(48)	22	(42)	32	(41)	31	(41)	*Reference*		*Reference*	
Male	33	(52)	31	(58)	46	(59)	44	(59)	1.2 (0.8–1.8)		1.1 (0.7–1.7)	
Age at most recent audiogram										**.019**		**.013**
<10 years	23	(36)	24	(45)	19	(24)	15	(20)	*Reference*		*Reference*	
10–15 years	25	(39)	16	(30)	34	(44)	33	(44)	1.8 (1.1–3.1)		2.5 (1.3–4.9)	
>15 years	16	(25)	13	(25)	25	(32)	27	(36)	2.1 (1.2–3.6)		3.0 (1.3–7.0)	
Age at cancer diagnosis										**.008**		**<.001**
<5 years	22	(34)	24	(45)	24	(31)	42	(56)	2.1 (1.3–3.5)		5.4 (2.5–12.0)	
5–9 years	15	(23)	8	(15)	24	(31)	20	(27)	1.9 (1.1–3.4)		2.5 (1.3–5.1)	
10–18 years	27	(42)	21	(40)	30	(38)	13	(17)	*Reference*		*Reference*	
Period of cancer diagnosis										**<.001**		**.001**
1990–1995	6	(9)	5	(9)	13	(17)	24	(32)	5.2 (2.6–10.6)		4.8 (2.1–11.0)	
1996–2001	17	(27)	11	(21)	23	(29)	24	(32)	2.4 (1.3–4.4)		1.7 (0.8–3.3)	
2002–2007	19	(30)	20	(38)	24	(31)	19	(25)	1.7 (1.0–3.0)		1.3 (0.7–2.4)	
2008–2014	22	(34)	17	(32)	18	(23)	8	(11)	*Reference*		*Reference*	
Treatments												
Cumulative cisplatin dose										**<.001**		**<.001**
No cisplatin (carboplatin only)	24	(38)	25	(47)	5	(6)	8	(11)	*Reference*		*Reference*	
≤300 mg/m^2	10	(16)	7	(13)	17	(22)	17	(23)	4.1 (2.1–8.2)		5.6 (2.2–14.1)	
301–450 mg/m^2	7	(11)	7	(13)	32	(41)	25	(33)	5.9 (3.1–11.1)		17.0 (6.2–46.8)	
>450 mg/m^2	23	(36)	14	(26)	24	(31)	25	(33)	2.9 (1.6–5.3)		13.5 (4.7–38.8)	

(Continues)

TABLE 3 (Continued)

	No hearing loss (Münster grade 0) $n = 64$		Mild hearing loss (Münster grade 1) $n = 53$		Moderate hearing loss (Münster grade 2) $n = 78$		Severe hearing loss (Münster grades 3 and 4) $n = 75$		Univariable		Multivariable	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	OR[c] (95% CI)	*p*-Value[d]	OR[c] (95% CI)	*p*-Value[d]
Cumulative carboplatin dose										**.011**		.106
No carboplatin (cisplatin only)	37	(58)	23	(43)	53	(68)	41	(55)	*Reference*		*Reference*	
<1500 mg/m^2	4	(6)	4	(8)	9	(12)	12	(16)	1.8 (0.9–3.8)		2.4 (0.9–6.3)	
1500–3000 mg/m^2	12	(19)	12	(23)	13	(17)	16	(21)	1.0 (0.6–1.7)		2.8 (1.1–6.7)	
>3000 mg/m^2	11	(17)	14	(26)	1	(1)	6	(8)	0.4 (0.2–0.8)		2.5 (0.8–7.6)	
Missing[e]	–	–	–	–	2	(3)	–	–	–		–	
Cranial radiation										**<.001**		**<.001**
No	54	(84)	39	(74)	41	(53)	38	(51)	*Reference*		*Reference*	
Yes	10	(16)	14	(26)	37	(47)	37	(49)	2.9 (1.8–4.6)		4.4 (2.5–7.8)	
HSCT										**<.001**		**.049**
No	62	(97)	49	(92)	75	(96)	58	(77)	*Reference*		*Reference*	
Yes	2	(3)	4	(8)	3	(4)	17	(23)	5.0 (2.2–11.7)		2.7 (1.0–7.2)	

Abbreviation: HSCT, hematopoietic stem cell transplantation.

[a]Ordering: no (Münster grade 0), mild (Münster grade 1), moderate (Münster grades 2a–2c), and severe hearing loss (Münster grade ≥3).

[b]Risk factors associated with higher severity grades of hearing loss at $p < .05$ were included in the multivariable analyses. Sex, age at most recent audiogram, and age at cancer diagnosis were included in the multivariable model independent of the strength of the association in the respective univariable model.

[c]Odds ratio from univariable and multivariable ordered logistic regression models: OR < 1 indicates that "no hearing loss" is more likely. OR > 1 indicates that higher values on the explanatory variable increase the likelihood of "mild/moderate/severe hearing loss".

[d]Global *p*-value calculated from likelihood-ratio test.

[e]Childhood cancer survivors (CCS) with missing data for cumulative carboplatin doses ($n = 2$) were excluded from the regression analysis.

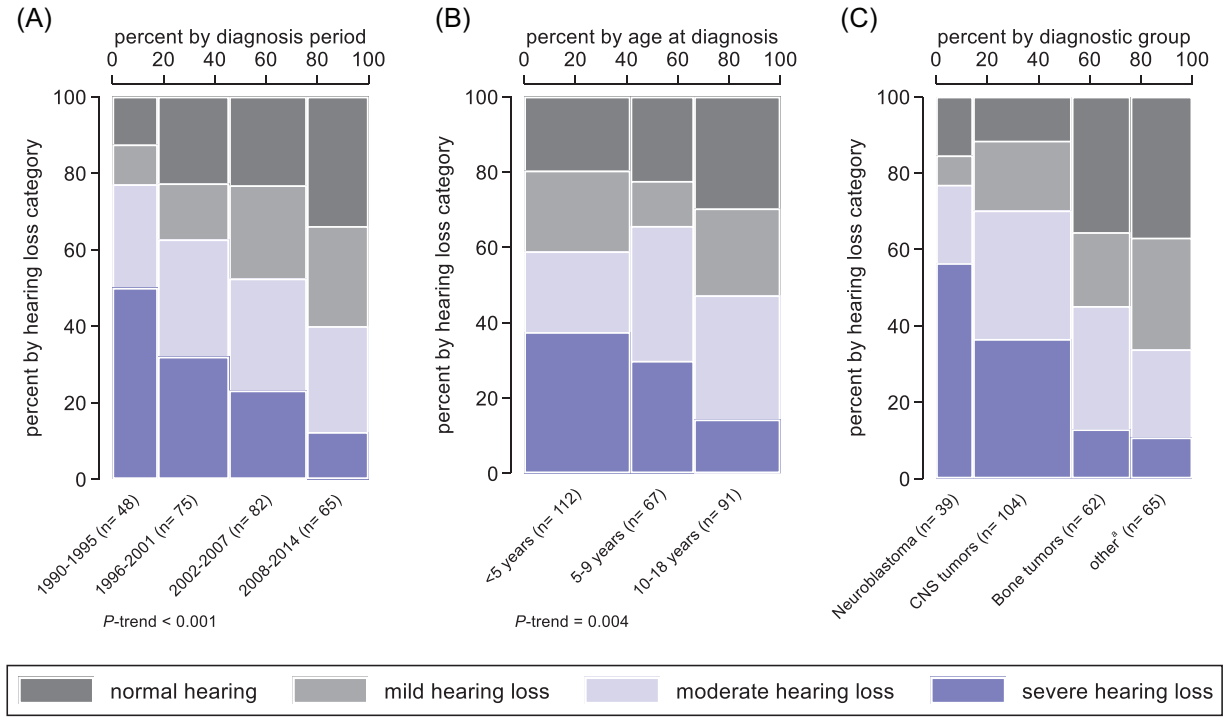

FIGURE 2 Prevalence of mild (Münster grade 1), moderate (Münster grades 2a-2c), and severe hearing loss (Münster grade ≥3) at most recent audiogram stratified by (A) cancer diagnosis period, (B) age at cancer diagnosis, and (C) diagnostic group ($N = 270$). Each column corresponds to a category of the variables A, B, and C. The width of the columns represents the proportion of childhood cancer survivors (CCS) in each category within A, B, and C. The height of each colored tile represents the proportion of CCS within a hearing loss category. Raw data of the figure are shown in Table S1. [a]Other diagnostic groups include: retinoblastoma ($n = 5$), renal tumors ($n = 6$), hepatic tumors ($n = 15$), soft tissue and other extraosseous sarcoma ($n = 12$), and germ cell tumors ($n = 27$)

Risk factors for a higher severity of hearing loss were young age (<5 years) at cancer diagnosis, treatment in earlier time period, high cumulative cisplatin dose, concomitant CRT, and HSCT (with borderline significance). Young age at cancer diagnosis,[8,13,18,21,42,45] high cumulative cisplatin dose,[8,13,18,21,42,45] concomitant CRT,[9,14,18] and HSCT[36] have also been identified as risk factors in previous studies. A common feature of these studies is the use of a binary definition for hearing loss.[8,18,21] The lack of a commonly agreed definition of hearing loss between studies and the existence of various ototoxicity grading scales[1] make comparisons between studies difficult. Only two studies differentiated several severity grades of hearing loss in their analysis, and only one of them included year of cancer diagnosis in a subanalysis.[13,35] Camet and colleagues found no effect of year at cancer diagnosis on hearing loss.[13] We found a higher severity of hearing loss among children treated in earlier years. Modern radiotherapeutic techniques using proton radiation instead of photon increasingly since 1996 with sparing of the inner ear,[46] more meticulous screening for hearing loss with a subsequent switch from cisplatin to carboplatin during treatment in affected children, and variation in dosing schedules such as rapid COJEC induction in more recent treatment protocols with reduced cisplatin cumulative doses[13,18] likely explain these findings. An alternative hypothesis could be the occurrence of late-onset hearing loss among CCS diagnosed in earlier periods.[2,12,47] However, our study was adjusted for age at most recent audiogram, suggesting that time period of cancer treatment remains an important predictor.

We found that CCS with a cumulative cisplatin dose of 301–450 mg/m^2 had the highest risk of hearing loss, while a cumulative cisplatin dose greater than 450 mg/m^2 did not further increase risk. This has been seen in other studies, and it could be explained by a cisplatin dose reduction or switch to carboplatin among patients with already occurring ototoxicity during cancer treatment.[9,48] Doses of carboplatin were not associated significantly with the severity of hearing loss in our study. Carboplatin is less ototoxic than cisplatin, but the literature is conflicting. Studies[11,19] focusing on specific diagnostic groups, such as retinoblastoma and neuroblastoma, observed an association with carboplatin, while three other studies[8,13,49] with large sample sizes and more heterogeneous study populations did not.

In conclusion, our results show that the burden of hearing loss after platinum-based chemotherapy remains high despite the decrease seen over the last decades. CCS treated at a young age with high cumulative doses of cisplatin and concomitant CRT are particularly at risk. Even if it is not a life-threatening late effect, hearing loss can have negative consequences on the lives of affected individuals.[5–7] Our findings suggest that monitoring the hearing function among this vulnerable population of CCS should be continued beyond the end of cancer treatment.[4]

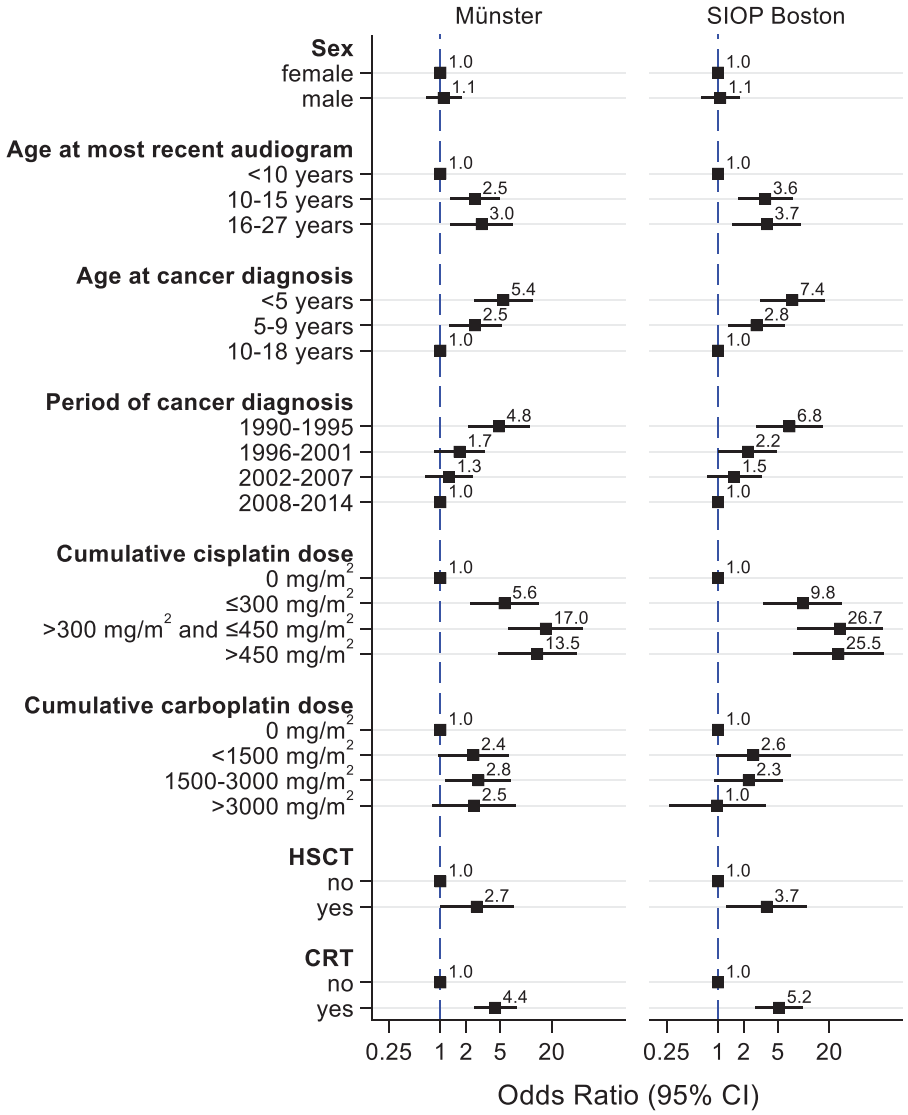

FIGURE 3 Comparison of the multivariable regression models using the Münster (left side) or SIOP Boston (right side) Ototoxicity Scale to define the outcome. For each included explanatory variable with its subcategories on the vertical axis, the odds ratio (OR) and the 95% confidence interval (CI) are displayed. The blue dotted line in the middle represents an OR of 1 meaning no effect on the risk for a higher severity grade of hearing loss. Abbreviations: HSCT, hematopoietic stem cell transplantation; CRT, cranial radiation therapy

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[Correction added on 30th June 2022, after first online publication: CSAL funding statement has been added].

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the information of this manuscript were accessed on secured servers of the Institute of Social and Preventive Medicine at the University of Bern. Individual-level sensitive data

can only be made available for researchers who fulfil the respective legal requirements. All data requests should be communicated to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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