original reports

Patient-Reported Functional Impairment Due to Hearing Loss and Tinnitus After Cisplatin-Based Chemotherapy

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abstract

PURPOSE Cisplatin is widely used and highly ototoxic, but patient-reported functional impairment because of cisplatin-related hearing loss (HL) and tinnitus has not been comprehensively evaluated.

PATIENTS AND METHODS Testicular cancer survivors (TCS) given first-line cisplatin-based chemotherapy completed validated questionnaires, including the Hearing Handicap Inventory for Adults (HHIA) and Tinnitus Primary Function Questionnaire (TPFQ), each of which quantifies toxicity-specific functional impairment. Spearman correlations evaluated associations between HL and tinnitus severity and level of functional handicap quantified with the HHIA and TPFQ, respectively. Associations between HL or tinnitus and five prespecified adverse health outcomes (cognitive dysfunction, fatigue, depression, anxiety, and overall health) were evaluated.

RESULTS HL and tinnitus affected 137 (56.4%) and 147 (60.5%) of 243 TCS, respectively. Hearing aids were used by 10% TCS (14/137). Of TCS with HL, 35.8% reported clinically significant functional impairment. Severe HHIA-assessed functional impairment was associated with cognitive dysfunction (odds ratio [OR], 10.62; $P < .001$), fatigue (OR, 5.48; $P = .003$), and worse overall health (OR, 0.19; $P = .012$). Significant relationships existed between HL severity and HHIA score, and tinnitus severity and TPFQ score ($P < .0001$ each). TCS with either greater hearing difficulty or more severe tinnitus were more likely to report cognitive dysfunction (OR, 5.52; $P = .002$; and OR, 2.56; $P = .05$), fatigue (OR, 6.18; $P < .001$; and OR, 4.04; $P < .001$), depression (OR, 3.93; $P < .01$; and OR, 3.83; $P < .01$), and lower overall health (OR, 0.39; $P = .03$; and OR, 0.46; $P = .02$, respectively).

CONCLUSION One in three TCS with HL report clinically significant functional impairment. Follow-up of cisplatin-treated survivors should include routine assessment for HL and tinnitus. Use of the HHIA and TPFQ permit risk stratification and referral to audiologists as needed, since HL adversely affects functional status and is the single largest modifiable risk factor for cognitive decline and dementia in the general population.

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INTRODUCTION

Cisplatin is one of the most ototoxic drugs in clinical use,[1,2] causing permanent, bilateral sensorineural hearing loss (HL) in up to 80% of cancer survivors,[3-6] with many experiencing tinnitus.[7,8] Despite recognition of cisplatin's ototoxicity over 40 years ago[9] and its retention in the cochlea indefinitely,[10] to our knowledge, no study has quantified its impact on the functional status of cancer survivors using validated, otologic-specific patient-reported outcome measures. In-depth investigations of common treatment toxicities are increasingly recognized as important in survivorship follow-up care.[11]

In the general population, HL begins in midlife,[12,13] with two thirds of individuals age ≥ 70 years having bilateral HL,[13] but for cancer survivors where treatment occurs earlier in life, cisplatin-related ototoxicity can exacerbate age-related HL.[3] Testicular cancer (TC) is one example, with a median diagnosis age of only 30 years,[14] and with TC the leading malignancy among men age 20-39 years.[15] Because of the effectiveness of cisplatin-based chemotherapy (CBCT), overall 10-year relative survival rates now exceed 95%.[14] Thus, TC survivors (TCS) are at risk for both short- and long-term adverse CBCT-related effects,[16] including HL and tinnitus, with no preventive or protective measures available. The sudden development of HL can be devastating,[17,18] and often more consequential than the slow progression of age-related HL. HL, even with a late age at onset, is significantly related to increased risks of cognitive decline and dementia,[19-23] decreased health-related quality of life,[24-27] poor mental and physical functioning,[28-32] and increased social

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Cisplatin is widely used and highly ototoxic, but patient-reported functional impairment because of cisplatin-related hearing loss (HL) and tinnitus has not been comprehensively evaluated. We quantified the impact of ototoxicity using validated, otologic-specific patient-reported outcomes: the Hearing Handicap Inventory for Adults, and Tinnitus Primary Function Questionnaire. These provide quantitative clinically actionable scores that can be used for risk stratification.

Knowledge Generated

Clinically significant functional impairments attributed to cisplatin-related HL and tinnitus were reported by 36% and 44% testicular cancer survivors, respectively. Significant relationships existed between HL severity and Hearing Handicap Inventory for Adults score, and tinnitus severity and Tinnitus Primary Function Questionnaire score.

Relevance *(M.A. Carducci)*

Attention to survivorship issues such as HL after platinum treatment for germ cell cancers is essential and includes follow-up with audiology, patient education, and thorough survivorship plans highlighting impact of HL.*

*Relevance section written by Michael A. Carducci, MD, FACP, FASCO.

isolation.[33-36] Tinnitus can lead to further social isolation, increased stress, anxiety, and, in extreme cases, mental health sequalae such as suicide.[37,38]

Nonetheless, to our knowledge, no investigation to date has comprehensively evaluated and quantified the effect of CBCT-associated ototoxicity on functional status in adult-onset cancer survivors.[16] To address this important gap, we quantified severity and administered HL- and tinnitus-specific handicap patient-reported measures, along with other validated questionnaires,[39-41] to a subset of TCS in a large multicenter investigation (The Platinum Study).[3,42,43] These HL- and tinnitus-specific questionnaires are unique in asking patients to partition functional deficits into those directly attributable to each toxicity and quantify them.[44,45] Resultant scores can then be used clinically to accurately risk-stratify patients for audiologic and other interventions.

PATIENTS AND METHODS

Patients

The Platinum Study enrolled cisplatin-treated TCS at eight cancer centers (2012-2018).[3,42,43] At enrollment, participants completed questionnaires and underwent physical examinations and extensive audiologic testing.[3,42,43,46,47] Administration of a subsequent survey to TCS enrolled at Indiana University, University of Pennsylvania, University of Rochester, Dana-Farber Cancer Institute, and Memorial Sloan Kettering Cancer Center was approved by the appropriate institutional review boards. This report includes 243 TCS with complete surveys through February 27, 2022. Standardized questionnaires collected demographic and clinical data, including information on medical history, lifestyle, and comorbidities. Validated instruments collected outcome data,[39-41,48-58] with questions and scoring criteria in Appendix 1 (online only).

Identifying Patients With HL and Tinnitus

HL was ascertained as a binary variable using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy-20 Scale[40]; Scale for Chemotherapy-Induced Long-Term Neurotoxicity (SCIN)[39]; and questions regarding hearing aid use, and difficulty hearing in crowds (Appendix 1). HL severity was quantified with, "During the past 4 weeks, did you have difficulty hearing?" with responses of not at all, a little, quite a bit, and very much.[40] Tinnitus was ascertained as a binary variable by patients describing ringing or buzzing or with questions in the SCIN,[39] which also quantified severity, "Have you suffered in the last 4 weeks from ringing or buzzing in your ears (ie, tinnitus)?" with responses of not at all, a little, quite a bit, and very much.[39]

Effect of Severity of HL or Tinnitus on Patient-Reported Functional Status

TCS with HL were administered the Hearing Handicap Inventory for Adults (HHIA),[45,59-62] a 25-item self-assessment quantifying the impact of HL, with 13 questions assessing emotional effects and 12 questions assessing social effects (see Appendix 2 [online only] for instrument validity, questions/scoring). Overall HHIA scores range from 0% to 100% (higher scores indicate greater handicap attributable to HL) and were grouped using standard clinical categories: none/minimal, 0%-16%; mild/moderate, 17%-42%; and severe, 43%-100%.[45,62] Patients with mild/moderate or greater handicap are typically referred for audiologic evaluation/treatment.

TCS with tinnitus were administered the Tinnitus Primary Function Questionnaire (TPFQ),[44] a 20-item self-assessment quantifying tinnitus' impact on four functional subdomains: concentration, emotion, hearing, and

sleep (see Appendix 3 [online only] for instrument validity, questions/scoring). Subdomain and overall scores range from 0% to 100% (higher scores indicate greater handicap attributable to tinnitus). Standard clinical categories were used to group scores: none/minimal, 0%-16%; mild/moderate, 17%-42%; and severe, 43%-100%.[63,64] Ratings of mild/moderate or greater handicap are considered clinically actionable, with patients referred for available interventions.

Effect of Severity of HL or Tinnitus on Patient-Reported Adverse Health Outcomes

We identified five patient-reported adverse health outcomes (AHOs), a priori, for which to evaluate relationships with HL and tinnitus: cognitive dysfunction, fatigue, anxiety, depression, and overall health (see Appendix 1 for definitions/scoring). For all TCS, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy 20-Item Scale[40] and SCIN[39] severity grading methods were used: not at all, a little, or quite a bit/very much. Quite a bit and very much were combined for modeling to increase precision and because they exhibited similar effect sizes. For TCS with HL and tinnitus, we also evaluated the HHIA and TPFQ clinical ratings (none/minimal, mild/moderate, and severe) and patient-reported AHOs.

Statistical Analyses

Descriptive statistics are provided as frequencies (proportions) for categorical variables or medians (interquartile range) for continuous variables. Logistic (binary or multinomial) or linear regression, as appropriate, were applied to bivariate comparisons. We conducted Spearman correlations between (1) HL severity and audiometrically measured HL, tinnitus severity, and HHIA handicap scores (total, subdomains); and (2) tinnitus severity and TPFQ handicap scores (total, subdomains). To evaluate associations of HL severity, tinnitus severity, HHIA, and TPFQ scores with prespecified AHOs, we performed multivariable regression analyses adjusted for age, body mass index, cumulative cisplatin dose, years since chemotherapy, tobacco use (never/ever), and hypertension.[3,43,65,66] Specifically, binary logistic regression was used for presence/absence of cognitive dysfunction, fatigue, anxiety, and depression, whereas *partial* proportional odds logistic regression was used for overall health (dependent variables). In *partial* proportional odds, ordered logit functions are used, except for covariates violating the proportion odds assumption for which multinomial functions are used. For covariates under the ordered logit relationship, a single odds ratio (OR) describes the assumed constant odds across the overall health categories. When the proportional odds assumption was violated for TPFQ score (a primary independent variable), overall health was dichotomized and binary logistic regression used.

RESULTS

Table 1 presents clinical and sociodemographic characteristics for all TCS and subgroups with HL or tinnitus. Among 243 TCS (median age at evaluation, 46 years [interquartile range, 38-53 years]), HL and tinnitus were reported by 137 (56.4%) and 147 (60.5%), respectively. Only 68 (28.0%) of TCS reported neither HL or tinnitus, and 109 (44.9%) reported both.

HL Severity

TCS with self-reported HL as a binary variable (n = 137) rated the severity of HL in the past 4 weeks as not at all (12.4%), a little (62.1%), quite a bit (12.4%), or very much (13.1%; Table 2). HL severity was significantly associated with audiometrically defined HL ($P < .001$), documenting participants' ability to accurately self-assess HL. For TCS with very much self-reported HL, audiometric results were consistent with moderately severe HL,[47] and 50% (9/18) used hearing aids.

All 137 TCS with HL were administered the HHIA, with a 99% completion rate (n = 136), resulting in 21 reporting mild/moderate overall handicap and 28 reporting severe overall handicap attributed to HL. Highly significant correlations ($P < .0001$ each) existed between greater HL severity and higher scores on the HHIA social and emotional subdomains (Spearman's rho = 0.68 and 0.66, respectively). Among TCS with either quite a bit or very much difficulty hearing, the overall degree of impairment ascribed to HL was noted as severe by 58.8% and 83.3%, respectively. A highly significant positive correlation existed between greater HL severity and worse overall handicap (Spearman's rho = 0.68; $P < .0001$; Fig 1A).

Tinnitus Severity

TCS with tinnitus described its severity in the past 4 weeks as a little (45.6%), quite a bit (27.9%), or very much (23.8%). Given sparse numbers (n = 4) in not at all, this category was combined with a little (Table 3). Worse tinnitus severity was significantly associated with worse HL severity (Spearman's rho = 0.48, $P < .0001$). TCS with tinnitus described as quite a bit or very much were older at survey completion ($P = .004$), had greater audiometrically defined HL ($P < .001$), had longer time since chemotherapy ($P = .04$), and had greater hearing aid use ($P = .001$).

All 147 TCS with tinnitus were administered the TPFQ, with 65 (44.2%) reporting a clinically actionable overall handicap of mild/moderate or severe. Worse tinnitus severity was significantly correlated (all $P < .0001$) with worse handicap in each TPFQ subdomain: concentration (Spearman's rho = 0.47), emotion (Spearman's rho = 0.57), hearing (Spearman's rho = 0.49), and sleep (Spearman's rho = 0.43), and overall (Spearman's rho = 0.55; Fig 1B). The TPFQ overall handicap attributed to tinnitus was rated

TABLE 1. Clinical Features and Sociodemographic Characteristics for 243 Survivors of Cisplatin-Treated Germ Cell Tumors

Characteristic	Total Population (N = 243)	No HL and No Tinnitus (n = 68)	HL (n = 137)[a]	Tinnitus (n = 147)[b]
Clinical characteristics				
Age at diagnosis, years	31 (25-39)	31 (25-38)	32 (25-41)	31 (25-40)
Age at survey completion, years	46 (38-53)	43 (37-52)	48 (40-55)	48 (38-53)
< 39	77 (31.7)	26 (38.2)	33 (24.1)	43 (29.2)
40-49	77 (31.7)	22 (32.4)	45 (32.8)	45 (30.6)
50-59	57 (23.5)	13 (19.1)	36 (26.3)	37 (25.2)
60+	32 (13.2)	7 (10.3)	23 (16.8)	22 (15.0)
BMI, kg/m^2[c]	27 (24-30)	27 (25-31)	27 (24-30)	27 (24-30)
Site[d]				
Testis	196 (83.1)	56 (86.2)	107 (79.9)	114 (79.2)
Extragonadal	40 (16.9)	9 (13.8)	27 (20.1)	30 (20.8)
CBCT[e]				
BEP × 3	132 (54.3)	45 (66.2)	69 (50.4)	74 (50.3)
BEP × 4	45 (18.5)	10 (14.7)	27 (19.7)	33 (22.4)
EP × 4	29 (11.9)	5 (7.4)	22 (16.1)	16 (10.9)
Other	37 (15.2)	8 (11.8)	19 (13.9)	24 (16.3)
Cumulative cisplatin dose, mg/m^2[f]	300 (300-400)	300 (300-400)	300 (300-400)	300 (300-400)
< 300	19 (7.9)	5 (7.4)	11 (8.1)	11 (7.6)
300	122 (50.8)	43 (63.2)	63 (46.7)	66 (45.5)
301-399	8 (3.3)	2 (2.9)	2 (1.5)	6 (4.1)
400+	91 (37.9)	18 (26.5)	59 (43.7)	62 (42.8)
Time from chemotherapy completion to survey, years[g]	10.7 (6.9-17.6)	9.4 (6.6-15.4)	12.9 (7.1-19.2)	11.2 (6.8-18.8)
< 5	20 (8.2)	9 (13.2)	8 (5.8)	11 (7.5)
5-9	89 (36.6)	25 (38.2)	43 (31.4)	52 (35.4)
10-14	52 (21.4)	15 (22.1)	31 (22.6)	31 (21.1)
15-19	39 (16.1)	9 (13.2)	25 (18.2)	23 (15.6)
20+	43 (17.7)	9 (13.2)	30 (21.9)	30 (20.4)
Sociodemographic characteristics				
Race[h]				
White	231 (95.9)	67 (98.5)	130 (97.0)	140 (95.2)
Other	9 (3.8)	1 (1.5)	4 (3.0)	7 (4.8)
Marital status[i]				
Not married	43 (17.9)	9 (13.4)	27 (20.0)	28 (19.3)
Married/living as married	197 (82.1)	58 (86.6)	108 (80.0)	117 (80.7)
Education[j]				
Not college graduate	51 (21.3)	11 (16.2)	36 (27.1)	35 (24.5)
College or postgraduate	188 (78.7)	57 (83.8)	97 (72.9)	108 (75.5)
Health behaviors				
Tobacco use[k]				
Never	166 (74.8)	53 (81.5)	83 (68.0)	96 (73.8)
Former	53 (23.9)	11 (16.9)	37 (30.3)	33 (25.4)
Current	3 (1.4)	1 (1.5)	2 (1.6)	1 (0.8)
Average No. of alcoholic drinks				
Rarely/never	62 (25.5)	17 (25.0)	36 (26.3)	42 (28.6)
1-3/mo	31 (12.8)	13 (19.1)	13 (9.5)	17 (11.6)

(continued on following page)

TABLE 1. Clinical Features and Sociodemographic Characteristics for 243 Survivors of Cisplatin-Treated Germ Cell Tumors (continued)

Characteristic	Total Population (N = 243)	No HL and No Tinnitus (n = 68)	HL (n = 137)[a]	Tinnitus (n = 147)[b]
1-6/wk	115 (47.3)	32 (47.1)	61 (44.5)	63 (42.9)
1+ per day	35 (14.4)	6 (8.8)	27 (19.7)	25 (17.0)
Physical activity				
Moderate (3 to < 6 METs)	232 (95.5)	67 (98.5)	129 (94.2)	137 (93.2)
Vigorous (6+ METs)	136 (56.0)	40 (58.8)	71 (51.8)	77 (52.4)
Health history				
Hypertension	70 (28.8)	14 (20.6)	48 (35.0)	49 (33.3)
Hypercholesterolemia	88 (36.2)	17 (25.0)	63 (46.0)	62 (42.2)
Hearing-related health history				
Audiometry, geometric mean (dB HL)[l]	20 (11-34)	13 (9-22)	26 (15-50)	25 (14-46)
HL	137 (56.4)	0 (0.0)	137 (100.0)	109 (74.1)
Tinnitus	147 (60.5)	0 (0.0)	109 (79.6)	147 (100.0)
Noise exposure				
None	146 (60.1)	46 (67.6)	75 (54.7)	84 (57.1)
Work-related only	51 (21.0)	12 (17.6)	31 (22.6)	31 (21.1)
Non–work-related	21 (8.6)	5 (7.4)	13 (9.5)	13 (8.8)
Both	25 (10.3)	5 (7.4)	18 (13.1)	19 (12.9)

NOTE. Data are presented as median (interquartile range) or count (%), where the % are column percentages, unless otherwise noted in the table footnotes.

Abbreviations: BEP × 3, 3 cycles of bleomycin, etoposide, and cisplatin; BEP × 4, 4 cycles of bleomycin, etoposide, and cisplatin; BMI, body mass index; CBCT, cisplatin-based chemotherapy; EP × 4, 4 cycles of etoposide and cisplatin; HL, hearing loss; MET, metabolic equivalent task; SCIN, Scale for Chemotherapy-Induced Long-Term Neurotoxicity.

[a]Patients were classified with HL on the basis of affirmative responses to the European Organisation for Research and Treatment of Cancer Chemotherapy-Induced Peripheral Neuropathy 20 Scale,[39] SCIN,[38] or by answering yes to either hearing aid use or having difficulty hearing in crowds. See HL definition in Appendix 1.

[b]Patients were classified with tinnitus on the basis of the SCIN[38] or by indicating that they had symptoms of ringing or buzzing in their ears. See tinnitus definition in Appendix 1.

[c]One patient who did not answer had both HL and tinnitus.

[d]Six patients had multiple diagnoses: three patients with no HL and no tinnitus, three patients with HL, and two patients with tinnitus. One patient did not have these data available and had tinnitus but no HL.

[e]The percentage of patients receiving each of the indicated chemotherapy regimens is shown in the second column. Of 132 patients given BEP × 3, 69 (53%) had HL and 74 (56%) had tinnitus. Of the 45 patients given BEP × 4, 27 (60%) had HL and 33 (73%) had tinnitus. Of the 29 patients given EP × 4, 22 (76%) had HL and 16 (73%) had tinnitus. Of the 37 patients given other regimens, 19 (51%) had HL and 24 (65%) had tinnitus. In previous work, we showed dose-response relationships between cumulative amount of cisplatin and HL, specifically each 100 mg/m^2 increase in dose was accompanied by a 3.2-dB impairment in age-adjusted overall hearing threshold ($P < .001$).[3] The 5-day administration regimen was used for each of BEP × 3 and BEP × 4.[67] The regimen labeled as other includes 11 patients receiving BEP other than three or four cycles, four patients receiving EP other than four cycles, four patients receiving vincristine, ifosfamide, cisplatin × 4, 11 patients receiving other regimens containing ifosfamide, five patients receiving regimens containing carboplatin, and two patients receiving other cisplatin-based regimens. BEP × 3 also includes four patients receiving BEP × 2 + EP × 1 and one patient receiving BEP × 1 + EP × 2. BEP × 4 also includes nine patients receiving BEP × 3 + EP × 1, three patients receiving BEP × 2 + EP × 2, and four patients receiving BEP × 1 + EP × 3.

[f]Three patients were treated with carboplatin without cisplatin: two patients with HL and two patients with tinnitus.

[g]The percentage of patients completing the survey within each of the designated time frames is shown in the second column. Of all 20 patients who completed the survey within the < 5 year interval after chemotherapy, 8/20 (40%) had HL and 11/20 (55%) had tinnitus. Corresponding percentages of patients reporting HL and tinnitus, respectively, in the 5-9, 10-14, 15-19, and 20+ year intervals are as follows: 48% and 58%; 60% and 60%; 64% and 59%; and 70% and 70%, respectively.

[h]Three patients did not answer or preferred not to designate race: three patients with HL and none with tinnitus.

[i]Three patients did not answer or preferred not to designate marital status: one patient with no HL and no tinnitus, and two patients with both HL and tinnitus.

[j]Four patients with both HL and tinnitus did not answer or answered other with regard to educational status.

[k]Twenty-one patients did not answer the question with regard to tobacco use: three patients with no HL and no tinnitus, 15 patients with HL, and 17 patients with tinnitus.

[l]Quantitative audiometry was performed on patients a median of 6.2 years (range, 3.2-8.2 years; at the time of initial study enrollment)[3] before completion of the current survey. Geometric means designate air conduction thresholds at 4, 6, 8, 10, and 12 kHz. Forty-four patients did not complete audiometry: 13 with no HL and no tinnitus, 26 with HL, and 28 with tinnitus.

TABLE 2. HL Characteristics and Functional Impairment Because of HL for 137 Testicular Cancer Survivors Stratified by Severity Scaling of the EORTC-CIPN20

	During the Past 4 Weeks, Did You Have Difficulty Hearing? (n = 137)				
Characteristic	**Not At All (n = 17)[a]**	**A Little (n = 85)**	**Quite a Bit (n = 17)**	**Very Much (n = 18)**	***P*[b]**
Sociodemographic characteristics					
Age at survey completion, years	45 (41-52)	48 (39-55)	52 (45-64)	49 (44-57)	.060
Race, White[c]	16 (100.0)	79 (95.2)	17 (100.0)	18 (100.0)	.508
BMI, kg/m^2	28 (26-30)	26 (24-31)	28 (24-30)	28 (26-32)	.918
Health behaviors and history					
Tobacco use ever[d]	6 (37.5)	22 (28.6)	2 (13.3)	9 (64.3)	.204
Hypertension	5 (29.4)	26 (30.6)	10 (58.8)	7 (38.9)	.176
History of chemotherapy treatment					
Cumulative cisplatin dose, mg/m^2[e]	300 (300-400)	300 (300-400)	300 (300-400)	400 (300-400)	.093
Time since chemotherapy completion, years	12.2 (6.9-19.8)	12.9 (7.3-18.2)	15.9 (8.6-27.0)	11.1 (5.4-19.1)	.960
Auditory health history					
Audiometry, geometric mean (dB HL)[f]	18 (11-31)	21 (14-34)	49 (38-66)	57 (38-62)	< .001
ASHA HL category	Slight	Slight	Moderate	Moderately Severe	
Tinnitus	10 (58.8)	65 (76.5)	17 (100.0)	17 (94.4)	.003
Hearing aid use[g]	0 (0.0)	1 (1.2)	4 (23.5)	9 (50.0)	< .001
Problem hearing words in crowds[h]					.007
Yes	14 (82.4)	43 (51.2)	17 (100.0)	17 (94.4)	
No/not sure	3 (17.6)	41 (48.8)	0 (0.0)	1 (5.6)	
Hearing Handicap Inventory-Adult[i]					
Overall score (0-100)	2 (0-6)	6 (2-12)	46 (28-54)	68 (50-86)	< .001
None/minimal handicap	16 (94.1)	69 (82.1)	2 (11.8)	0 (0.0)	
Mild/moderate handicap	1 (5.9)	12 (14.3)	5 (29.4)	3 (16.7)	
Severe handicap	0 (0.0)	3 (3.6)	10 (58.8)	15 (83.3)	
Social subscale (0-48)	2 (0-4)	2 (0-6)	22 (14-26)	32 (26-42)	< .001
None/minimal handicap	16 (94.1)	73 (86.9)	0 (0.0)	0 (0.0)	
Mild/moderate handicap	1 (5.9)	8 (9.5)	8 (47.1)	4 (22.2)	
Severe handicap	0 (0.0)	3 (3.6)	9 (52.9)	14 (77.8)	
Emotional subscale (0-52)	0 (0-4)	2 (0-8)	24 (10-30)	36 (22-44)	< .001
None/minimal handicap	17 (100.0)	68 (81.0)	4 (23.5)	1 (5.6)	
Mild/moderate handicap	0 (0.0)	14 (16.7)	4 (23.5)	4 (22.2)	
Severe handicap	0 (0.0)	2 (2.4)	9 (52.9)	13 (72.2)	

NOTE. Data are presented as median (interquartile range) or count (%) for a given column, unless otherwise noted in the table footnotes. The HHIA survey was administered to 137 patients meeting criteria for HL in Appendix 1. In brief, these patients (1) reported having difficulty hearing during the past 4 weeks on the EORTC-CIPN20[39]; (2) reported having reduced hearing in the past 4 weeks on the SCIN[38]; or (3) answered yes to either hearing aid use or having difficulty hearing in crowds.

Abbreviations: ASHA, American Speech-Language-Hearing Association; BMI, body mass index; EORTC-CIPN20, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy 20-Item Scale; HHIA, Hearing Handicap Inventory for Adults; HL, hearing loss; SCIN, Scale for Chemotherapy-Induced Long-Term Neurotoxicity.

[a]Seventeen patients had HL on the basis of their response to the SCIN questionnaire[38] or they answered yes to hearing aid use or to having trouble hearing words in crowds; however, they answered the EORTC-CIPN-20 question,[39] "During the past 4 weeks, did you have difficulty hearing?" as not at all. On the basis of their affirmative responses to having HL, they were administered the HHIA, with their results included in the table.

[b]Unadjusted *P* values were calculated using logistic regression for dichotomous variables and linear regression for continuous variables, with severity of HL as the independent variable.

[c]Three patients did not specify race: one and two patients, respectively, in the not at all and a little categories.

[d]Fifteen patients did not specify tobacco use: one, eight, two, and four patients, respectively, in the not at all, a little, quite a bit, and very much categories.

[e]Two patients in this table were treated with carboplatin without cisplatin.

[f]Quantitative audiometry was performed on patients a median of 6.2 years (range, 3.2-8.2 years; at the time of initial enrollment)[3] before completion of the current survey. Geometric means are for air conduction thresholds at 4, 6, 8, 10, and 12 kHz. Twenty-six patients did not complete audiometry at enrollment: one, 17, four, and four patients, respectively, in the not at all, a little, quite a bit, and very much categories.

[g]One patient in the a little category did not specify hearing aid use.

[h]One patient in the a little category did not answer this question.

[i]Of the 137 patients administered the HHIA, 136 completed it; one patient with a little HL did not complete the HHIA.

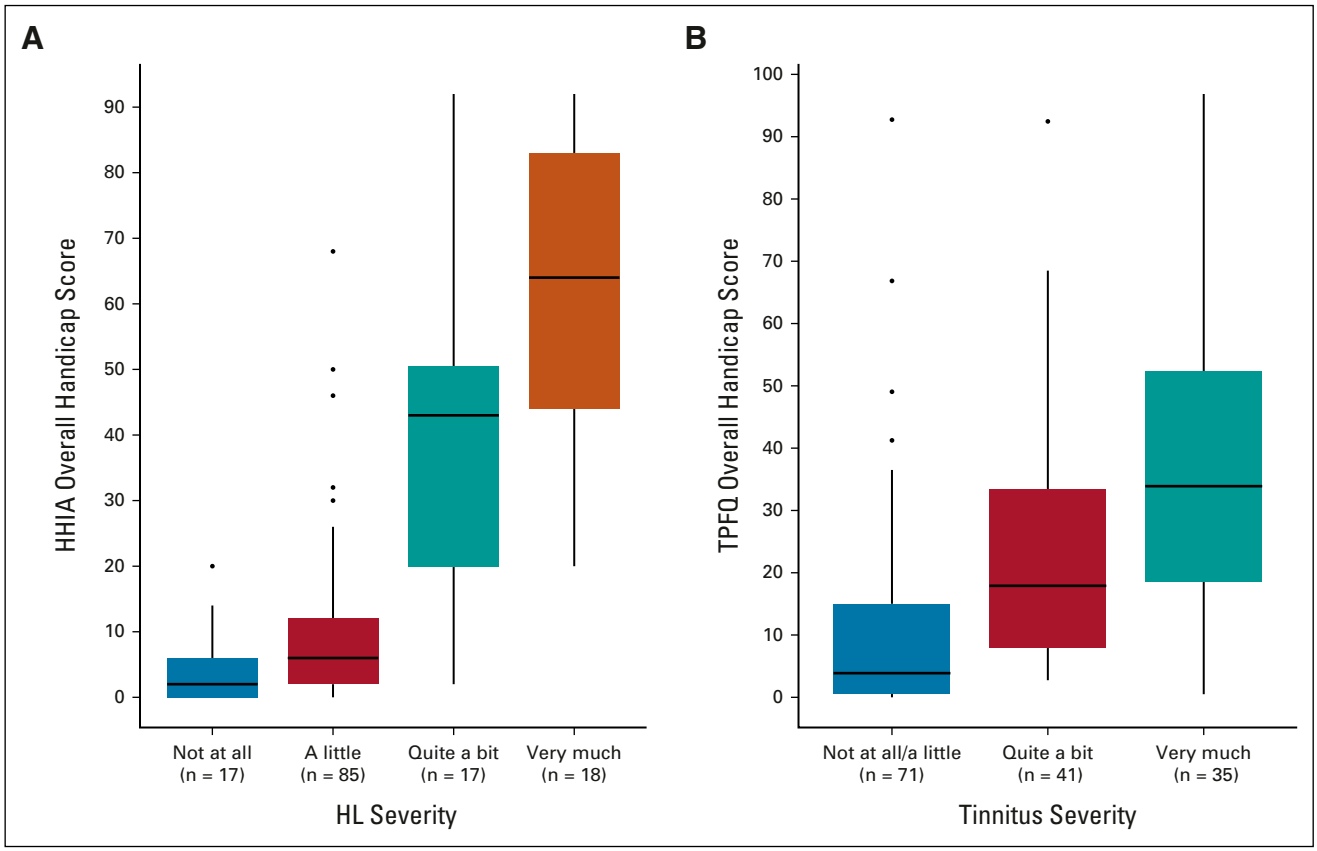

FIG 1. Correlation between various degrees of hearing loss and tinnitus and patient-reported functional impairment using the overall handicap scores in the Hearing Handicap Inventory for Adults (HHIA; A) and the Tinnitus Primary Frequency Questionnaire (TPFQ; B), respectively. Data are presented as box and whisker plot diagrams and correlation analysis using Spearman's rank correlation coefficient. The Spearman's correlation between (A) self-reported hearing loss severity and overall HHIA handicap is $\rho = 0.68$; $P < .001$ and between (B) self-reported tinnitus severity and overall TPFQ handicap is $\rho = 0.55$; $P < .001$. HHIA, Hearing Handicap Inventory for Adults; HL, hearing loss; TPFQ, Tinnitus Primary Function Questionnaire.

as severe by 14.6%, and 34.2% of TCS with tinnitus described as quite a bit or very much

Effect of Severity of HL or Tinnitus on Prespecified AHOs

Table 4 shows relationships between AHOs and the degree of hearing and tinnitus difficulty for all 243 TCS. Hearing difficulty was significantly related to cognitive dysfunction, fatigue, and depression. After covariate adjustment, increasing hearing difficulty, in particular quite a bit/very much versus not at all, remained significantly associated with cognitive dysfunction (OR, 5.52; $P = .002$), fatigue (OR, 6.18; $P < .001$), and depression (OR, 3.93; $P = .005$), as well as with worse overall health (proportional odds logistic OR, 0.39; $P = .029$), indicating greater HL was associated with lower odds of better overall health.

Tinnitus severity was significantly related to cognitive dysfunction, fatigue, and depression. After covariate adjustment, increasing tinnitus severity, in particular quite a bit/very much versus not at all, was significantly associated with each AHO: cognitive dysfunction (OR, 2.56; $P = .050$), fatigue (OR, 4.04, $P = .001$), depression (OR, 3.83, $P = .002$), and anxiety (OR, 2.36; $P = .038$). Greater tinnitus severity was also significantly associated with worse overall health (proportional odds logistic OR, 0.46; $P = .023$).

Effect of Clinically Scaled HHIA and TPFQ Results on Prespecified AHOs

Among TCS with HL, functional impairment because of HL quantified with the HHIA was significantly related to cognitive dysfunction and fatigue (Table 5). After covariate adjustment, severe hearing handicap (*v* none/minimal) remained significantly associated with both outcomes (OR, 10.62; $P < .001$ and OR, 5.48; $P = .003$, respectively), and with worse overall health (binary logistic OR, 0.19; $P = .012$).

Tinnitus handicap quantified with the TPFQ was significantly related to cognitive dysfunction, fatigue, anxiety, and overall health. After covariate adjustment, severe tinnitus handicap (*v* none/minimal) remained significantly associated with cognitive dysfunction (OR, 12.58; $P < .001$), fatigue (OR, 7.16; $P = .003$), and worse overall health (binary logistic OR, 0.15; $P = .007$).

TABLE 3. Tinnitus Characteristics and Functional Impairment Because of Tinnitus for 147 Testicular Cancer Survivors Stratified by Severity Category of the SCIN

	Have You Suffered in the Last 4 Weeks From Ringing or Buzzing in Your Ears (ie, tinnitus)? (n = 147)			
Characteristic	**Not At All/A Little[a] (n = 71)**	**Quite a Bit (n = 41)**	**Very Much (n = 35)**	***P*[b]**
Sociodemographic characteristics				
Age at diagnosis, years	30 (24-38)	31 (25-42)	32 (26-43)	.144
Age at survey completion, years	45 (36-52)	49 (39-61)	48 (43-58)	.005
Race, White	67 (94.4)	39 (95.1)	34 (97.1)	.544
BMI, kg/m^2	27 (24-30)	30 (24-33)	26 (24-29)	.794
Health behaviors and history				
Tobacco use, ever/current[c]	17 (25.8)	12 (32.4)	5 (18.5)	.650
Hypertension	21 (29.6)	15 (36.6)	13 (37.1)	.390
History of chemotherapy treatment				
Cumulative cisplatin dose, mg/m^{2}[,d]	300 (300-400)	300 (300-400)	400 (300-400)	.127
Time since chemotherapy completion, years	10.0 (6.6-16.5)	13.3 (7.0-20.5)	11.2 (8.6-22.9)	.042
Auditory health history				
Audiometry, geometric mean (dB)[e]	16 (9-24)	44 (21-55)	40 (26-58)	< .001
HL[f]	44 (62.0)	34 (82.9)	31 (88.6)	.002
Hearing aid use[g]	2 (2.9)	4 (9.8)	8 (22.9)	.003
Problem hearing words in crowds[h]				
Yes	24 (34.3)	23 (56.1)	26 (74.3)	< .001
No/not sure	46 (65.7)	18 (43.9)	9 (25.7)	
Tinnitus primary function questionnaire				
Overall handicap (0-100)[i]	4 (1-15)	18 (8-33)	34 (17-58)	< .001
None/minimal handicap	52 (76.5)	19 (46.3)	8 (22.9)	
Mild/moderate handicap	13 (19.1)	16 (39.0)	15 (42.9)	
Severe handicap	3 (4.4)	6 (14.6)	12 (34.2)	
Concentration subdomain (0-100)[j]	2 (0-17)	20 (4-40)	34 (18-60)	< .001
None/minimal handicap	51 (75.0)	17 (41.4)	8 (22.9)	
Mild/moderate handicap	11 (16.2)	15 (36.6)	12 (34.2)	
Severe handicap	6 (8.8)	9 (22.0)	15 (42.9)	
Emotion subdomain (0-100)[k]	6 (1-23)	27 (10-40)	41 (35-64)	< .001
None/minimal handicap	45 (66.2)	14 (34.2)	4 (11.4)	
Mild/moderate handicap	16 (23.5)	19 (46.3)	16 (45.7)	
Severe handicap	7 (10.3)	8 (19.5)	15 (42.9)	
Hearing subdomain (0-100)[l]	1 (0-13)	15 (2-30)	32 (8-60)	< .001
None/minimal handicap	55 (80.9)	20 (50.0)	9 (25.8)	
Mild/moderate handicap	9 (13.2)	15 (37.5)	13 (37.1)	
Severe handicap	4 (5.9)	5 (12.5)	13 (37.1)	
Sleep subdomain (0-100)[m]	0 (0-5)	4 (0-26)	14 (2-54)	< .001
None/minimal handicap	59 (88.0)	27 (65.8)	19 (54.3)	

(continued on following page)

TABLE 3. Tinnitus Characteristics and Functional Impairment Because of Tinnitus for 147 Testicular Cancer Survivors Stratified by Severity Category of the SCIN (continued)

	Have You Suffered in the Last 4 Weeks From Ringing or Buzzing in Your Ears (ie, tinnitus)? (n = 147)			
Characteristic	**Not At All/A Little[a] (n = 71)**	**Quite a Bit (n = 41)**	**Very Much (n = 35)**	***P*[b]**
Mild/moderate handicap	6 (9.0)	9 (22.0)	6 (17.1)	
Severe handicap	2 (3.0)	5 (12.2)	10 (28.6)	

NOTE. Data are presented as median (interquartile range) or count (%) for a given column, unless otherwise noted in the table footnotes. TPFQ survey results were collected for 147 patients reporting suffering any ringing or buzzing in your ears (ie, tinnitus) in the last 4 weeks, a question from SCIN,[38] or by indicating in a separate item that they had symptoms of ringing or buzzing in their ears (ie, tinnitus). See tinnitus definition in Appendix 1.

Abbreviations: BMI, body mass index; HL, hearing loss; SCIN, Scale for Chemotherapy-Induced Long-Term Neurotoxicity; TPFQ, Tinnitus Primary Function Questionnaire.

[a]Severity groups not at all and a little were combined because of only four patients reporting tinnitus severity as not at all. These four patients had reported having tinnitus in a separate item (ringing or buzzing in your ears [ie, tinnitus]) and were thus included in the subset administered the TPFQ.

[b]Unadjusted *P* values were calculated using logistic regression for dichotomous variables and linear regression for continuous variables, with severity of tinnitus as the independent variable.

[c]Seventeen patients did not answer: five patients in the not at all and a little severity groups, four patients in the quite a bit severity group, and eight patients in the very much severity group.

[d]Two patients in this table were treated with carboplatin without cisplatin.

[e]Quantitative audiometry was performed on testicular cancer survivors a median of 6.2 years (range, 3.2-8.2 years; at the time of initial enrollment)[3] before completion of the current survey. Geometric means are for air conduction thresholds at 4, 6, 8, 10, and 12 kHz. 28 patients did not complete audiometry at enrollment: 16 patients in the not at all and a little severity groups, five patients in the quite a bit severity group, and seven patients in the very much severity group.

[f]One patient in the not at all/a little category did not specify HL.

[g]One patient in the not at all/a little category did not specify hearing aid use.

[h]One patient in the not at all/a little category did not answer this question.

[i]Three patients had insufficient data across the four subdomains to estimate the total handicap.

[j]Three patients did not complete the concentration subdomain questions.

[k]Three patients did not complete the emotion subdomain questions.

[l]Four patients did not complete the hearing subdomain questions.

[m]Four patients did not complete the sleep subdomain questions.

DISCUSSION

To our knowledge, this is the first study to examine the toxicity-specific functional effect of cisplatin-associated HL and tinnitus, and the severity of these symptoms, in adult-onset cancer survivors. We provide evidence of the deleterious impact on social and emotional functioning directly related to HL and tinnitus in a well-characterized population. After CBCT, 56% of TCS report HL, and overall, one in five survivors with HL indicates a severe handicap in social and emotional functioning attributable to HL. The proportion of severe functional impairment increases to 83% among TCS who describe very much hearing difficulty. Tinnitus occurred in 60% of TCS and, similar to HL, a significant positive correlation existed between greater severity and worse overall handicap attributed to tinnitus. The overall degree of functional impairment because of tinnitus was described as severe by one in three TCS with very much tinnitus. Cognitive dysfunction, fatigue, depression, and lower overall health were significantly associated with both HL and tinnitus severity. These and other new findings are discussed below.

HL is the third most prevalent disability worldwide,[68,69] and associated with cognitive decline, fatigue, social isolation, depression, and other AHOs.[20,31,33,35,36,70,71] An estimated $750 billion US dollars is spent annually on 466 million people with disabling HL, with many cases developing gradually and age-related.[13] After CBCT, however, HL develops rapidly because of inner ear damage including the inner and outer sensory hair cells, spiral-ganglion neurons, stria vascularis, and injury to central auditory pathways.[1,72] The HL is permanent, becoming a chronic health condition.

Previously, we reported detailed audiometric findings in this well-characterized cohort,[3,46] including dose-response relationships with CBCT.[3] We now show the deleterious impact of ototoxicity on patient-reported functional status. Over 33% of TCS with HL indicated more than a mild handicap in social and emotional functioning attributable to HL. More than a mild handicap suggests significant hearing problems warranting diagnostic evaluation and clinical intervention.[73] In the general population, HL is associated with depression[74,75] and fatigue,[76,77] and our study demonstrates similar relationships in adult-onset cancer survivors. Nearly 40% of TCS with severe HL handicap quantified with the HHIA reported depression and 50% noted fatigue. HL-related listening fatigue is thought to be due to the increased cognitive load and extra effort needed to process speech, thereby depleting cognitive resources and resulting in fatigue.[78] Listening fatigue and increased

TABLE 4. Effect of Severity of HL or Tinnitus on AHOs and Overall Health Among 243 Survivors of Cisplatin-Treated Germ Cell Tumors

	Severity of HL (N = 243) During the Past 4 Weeks, Did You Have Difficulty Hearing?				Logistic Regression (AHO as dependent variable)[a,b]			
					A Little *v* Not At All		Quite a Bit/Very Much *v* Not At All	
Outcome	Not At All (n = 122)	A Little (n = 85)	Quite a Bit/Very Much (n = 35)	*P*[c]	OR (95%CI)	*P*	OR (95%CI)	*P*
AHO								
Cognitive dysfunction	10 (8.2)	9 (10.6)	12 (34.3)	.001	1.40 (0.53 to 3.72)	.496	5.52 (1.88 to 16.21)	.002
Fatigue	16 (13.1)	17 (20.0)	14 (40.0)	.004	2.22 (0.99 to 5.01)	.053	6.18 (2.19 to 17.41)	< .001
Depression	20 (16.4)	26 (30.6)	14 (40.0)	.005	2.25 (1.08 to 4.69)	.031	3.93 (1.50 to 10.28)	.005
Anxiety	25 (20.5)	23 (27.1)	11 (31.4)	.324	1.50 (0.74 to 3.06)	.259	1.31 (0.47 to 3.63)	.603
Overall self-reported health				.021	0.71 (0.39 to 1.30)	.268	0.39 (0.17 to 0.91)	.029
Excellent/very good	65 (53.3)	40 (47.1)	11 (31.4)					
Good	43 (35.2)	35 (41.2)	14 (40.0)					
Fair/poor	14 (11.5)	10 (11.8)	10 (28.6)					

	Severity of Tinnitus (N = 243) Have You Suffered in the Last 4 Weeks From Ringing or Buzzing in Your Ears (ie, tinnitus)?				Logistic Regression (AHO as dependent variable)[a,b]			
					A Little *v* Not At All		Quite a Bit/Very Much *v*. Not At All	
	Not At All (n = 100)	A Little (n = 67)	Quite a Bit/Very Much (n = 76)	*P*[c]	OR (95%CI)	*P*	OR (95%CI)	*P*
AHO								
Cognitive dysfunction	9 (9.0)	7 (10.4)	16 (21.1)	.057	1.23 (0.42 to 3.59)	.700	2.56 (0.999 to 6.57)	.050
Fatigue	12 (12.0)	12 (17.9)	24 (31.6)	.006	1.74 (0.70 to 4.33)	.236	4.04 (1.71 to 9.54)	.001
Depression	15 (15.0)	19 (28.4)	26 (34.2)	.008	3.07 (1.31 to 7.16)	.010	3.83 (1.66 to 8.85)	.002
Anxiety	18 (18.0)	21 (29.6)	23 (30.3)	.119	2.28 (1.02 to 5.06)	.044	2.36 (1.05 to 5.30)	.038
Overall self-reported health				.002	0.42 (0.21 to 0.82)	.012	0.46 (0.23 to 0.90)	.023
Excellent/very good	58 (58.0)	32 (47.8)	26 (34.2)					
Good	36 (36.0)	22 (32.8)	35 (46.1)					
Fair/poor	6 (6.0)	13 (19.4)	15 (19.7)					

NOTE. For multivariable regressions, the dependent variables are the prespecified AHO. Binary logistic regression was used for cognitive dysfunction, anxiety, depression, and fatigue. Partial proportional odds logistic regression was used for overall health. Each model was adjusted for variables that are known to be associated with HL and tinnitus severity: age (at survey completion), body mass index, cumulative cisplatin dose, years since chemotherapy, tobacco use (never/ever), and hypertension.[3,42,64,65]

Abbreviations: AHO, adverse health outcome; HL, hearing loss; OR, odds ratio.

[a]Analysis includes 218 patients with complete data for all variables in the model; 25 patients were excluded because of missing values in one or more variables.

[b]Analysis includes 219 patients with complete data for all variables in the model; 24 patients were excluded because of missing values in one or more variables.

[c]Unadjusted *P* values were calculated via likelihood ratio tests for the severity of HL or severity of tinnitus categorical variables in unadjusted binary logistic regression models for cognitive dysfunction, fatigue, depression, and anxiety. For overall health, unadjusted *P* values were calculated via likelihood ratio tests for the severity of HL or severity of tinnitus variables in unadjusted proportional odds logistic regression models.

cognitive load are hypothesized as one underlying mechanism explaining robust independent associations observed between HL and cognitive decline.[79] TCS with more severe HL handicap were also 10-fold more likely to indicate cognitive dysfunction than TCS with no/minimal handicap.

Despite recommendations for clinical intervention and the known AHOs related to untreated HL,[73,80] only 10% of TCS with HL used hearing aids, indicating that most TCS are not receiving treatment options. This low prevalence is alarming, considering robust evidence that hearing health care including hearing aids can reduce listening fatigue[76]

TABLE 5. Effect of Severity of Patient-Reported Functional Impairment Because of HL or Tinnitus on AHOs and Overall Health

	HHIA Total Score Group[a] (n = 136)				Logistic Regression (AHO as dependent variable)[b,c]			
					Mild/Moderate Handicap *v* None/Minimal		Severe Handicap *v* None/Minimal	
HL	None/Minimal Handicap (n = 87)	Mild/Moderate Handicap (n = 21)	Severe Handicap (n = 28)	*P*[d]	OR (95%CI)	*P*	OR (95%CI)	*P*
AHO								
Cognitive dysfunction	7 (8.0)	3 (14.3)	13 (46.4)	< .001	1.39 (0.25 to 6.14)	.679	10.62 (3.15 to 40.15)	< .001
Fatigue	14 (16.1)	3 (14.3)	14 (50.0)	.001	0.74 (0.14 to 2.83)	.679	5.48 (1.84 to 17.29)	.003
Depression	22 (25.3)	9 (42.9)	11 (39.3)	.170	2.71 (0.91 to 8.05)	.070	1.96 (0.68 to 5.52)	.205
Anxiety	17 (19.5)	8 (38.1)	10 (35.7)	.093	2.68 (0.81 to 8.69)	.099	1.85 (0.57 to 5.73)	.291
Overall self-reported health				.002				
Excellent/very good/good[e]	77 (88.5)	20 (95.2)	17 (60.7)		3.58 (0.5 to 79.51)	.286	0.19 (0.05 to 0.68)	.012
Poor/fair	10 (11.5)	1 (4.8)	11 (39.3)		Ref	—	Ref	—

	TPFQ Total Score Group[f] (n = 144)				Logistic Regression (AHO as dependent variable)[g]			
					Mild/Moderate Handicap *v* None/Minimal		Severe Handicap *v* None/Minimal	
Tinnitus	None/Minimal Handicap (n = 79)	Mild/Moderate Handicap (n = 44)	Severe Handicap (n = 21)	*P*[d]	OR (95%CI)	*P*	OR (95%CI)	*P*
AHO								
Cognitive dysfunction	6 (7.6)	5 (11.4)	12 (57.1)	< .001	1.46 (0.38 to 5.46)	.568	12.58 (3.42 to 51.58)	< .001
Fatigue	16 (20.3)	8 (18.2)	13 (61.9)	< .001	0.86 (0.29 to 2.42)	.783	7.16 (2.15 to 26.48)	.002
Depression	20 (25.3)	12 (27.3)	11 (52.4)	.062	0.88 (0.33 to 2.27)	.795	2.78 (0.84 to 9.41)	.095
Anxiety	21 (26.6)	10 (22.7)	12 (57.1)	.016	0.71 (0.26 to 1.84)	.490	1.81 (0.55 to 5.83)	.321
Overall self-reported health				.007				
Excellent/very good/good[h]	66 (83.5)	38 (86.4)	11 (52.4)		1.38 (0.40 to 5.39)	.618	0.15 (0.04 to 0.59)	.007
Poor/fair	13 (16.5)	6 (13.6)	10 (47.6)		Ref	—	Ref	—

Abbreviations: AHO, adverse health outcome; EORTC-CIPN20, European Organisation for Research and Treatment of Cancer Chemotherapy-Induced Peripheral Neuropathy 20 Scale; HHIA, Hearing Handicap Inventory for Adults; HL, hearing loss; OR, odds ratio; TPFQ, Tinnitus Primary Function Questionnaire.

[a]The HHIA survey was administered to 137 patients reporting having any hearing difficulty during the past 4 weeks from the EORTC-CIPN20 survey,[39] suffering any reduced hearing in the last 4 weeks from the SCIN,[38] or by answering yes to either hearing aid use or having difficulty hearing in crowds. See HL definition in Appendix 1. One patient reported a little HL on the EORTC-CIPN20, but did not complete the HHIA; thus, reported frequencies for the HHIA questions are based on 136 patients.

[b]For multivariable regressions, the dependent variables are the prespecified AHO. Binary logistic regression was used for cognitive function, anxiety, depression, fatigue, and overall health (excellent/very good/good *v* poor/fair). Each model was adjusted for variables that are known to associate with HL and tinnitus severity: age (at survey completion), body mass index, cumulative cisplatin dose, years since chemotherapy, tobacco use (never/ever), and hypertension.[3,42,64,65]

[c]Analysis includes 120 patients with complete data for all variables in the model; 16 patients were excluded because of missing values in one or more variables.

[d]Unadjusted *P* values were calculated via likelihood ratio tests for the HHIA and TPFQ score group categorical variables in unadjusted binary logistic regression models for cognitive dysfunction, fatigue, depression, anxiety, and overall health (excellent/very good/good *v* poor/fair).

[e]Good was combined with very good/excellent because (1) there were smaller sample sizes in this subsample analysis, (2) good behaved similarly to excellent/very good regarding ORs compared with fair/poor, and (3) the proportional odds assumption was violated for one of the outcomes in this table.

[f]TPFQ survey results were collected for 147 patients reporting suffering any ringing or buzzing in your ears (ie, tinnitus) in the last 4 weeks, a question from the SCIN,[38] or by indicating in a separate item that they had symptoms of ringing or buzzing in their ears (ie, tinnitus). See tinnitus definition in Appendix 1. Three patients had insufficient data across the four subdomains to estimate the total handicap; thus, reported frequencies are based on 144 patients.

[g]Analysis includes 125 patients with complete data for all variables in the model; 19 patients were excluded because of missing values in one or more variables.

[h]Good was combined with very good/excellent because (1) there were smaller sample sizes in this subsample analysis, (2) good behaved similarly to excellent/very good regarding ORs compared with fair/poor, and (3) the proportional odds assumption was violated for one of the outcomes in this table.

and depression,[74,75] and improve communication,[81] cognition,[19,74] and health-related quality of life.[82-84] In a 2017 Cochrane Review of five randomized controlled trials involving 825 older adults using hearing aids, Ferguson et al[84] reported large improvements in listening ability,[85,86] and a large beneficial effect on hearing-specific quality of life using the Hearing Handicap Inventory for the Elderly[60,87] compared with unaided/placebo conditions. HL is a modifiable chronic condition, and interventions must include evidence-based approaches with provision of hearing assistive technologies along with self-management support.[88] US adults face structural barriers to accessing hearing health care, including high costs and difficulty navigating the hearing health care system,[89] which may in part explain the low hearing aid use here. This low uptake is troubling, given the increasing amount of evidence that relates untreated HL in the general population to AHOs as well as to increased risks of dementia and cognitive decline.[22,23] In fact, untreated HL has been identified as the single largest modifiable risk factor for dementia,[22] and may be especially important as TCS become older and susceptible to additional age-related HL. Cognitive decline in older adults also results in negative relational, socioeconomic, and public health implications.[22,23]

Tinnitus affects 10%-15% of adults worldwide.[90] Severity is key to consider, as increasing tinnitus severity is strongly associated with AHOs.[91,92] Suffering from tinnitus is not the same as tinnitus perception,[91] and only 3%-5% of the general population actually suffers with tinnitus.[64,93] Neuroimaging has revealed that individuals reporting severe tinnitus have different brain activity and connectivity patterns.[94-96] We found a strong relationship between more severe tinnitus and cognitive dysfunction, fatigue, anxiety, depression, and overall health. The severity scaling of tinnitus on these relationships is noteworthy, as suffering related to tinnitus can result in social isolation, increased stress, and, in extreme cases, suicide.[37,38] We previously reported a significantly elevated two- to three-fold risk of prescription medications for anxiety and depression in TCS with tinnitus.[97]

Tinnitus severity was also significantly associated with greater TPFQ-quantified functional impairment. Among TCS with tinnitus, 45% indicated more than a mild/moderate degree of overall handicap attributable to tinnitus. There are no medicinal treatments for tinnitus; however, rehabilitative approaches may be beneficial and are often offered through a structured hierarchical manner to provide an individual patient-centered approach. If a patient presents with both HL and tinnitus, the provision of hearing aids can ameliorate not only HL, but often reduce tinnitus.[98,99] Effective psychologic treatments for tinnitus include cognitive-behavioral approaches.[100,101]

We provide evidence of the deleterious impact on social and emotional functioning related to HL and tinnitus in a well-characterized clinical TCS cohort. Strengths of our study include the homogenous CBCT, quantitative hearing assessments, and use of validated clinical instruments to quantify functional impairment attributable to HL and tinnitus. Given their efficacy, the HHIA and TPFQ are used worldwide and have been translated into multiple languages, including Spanish, Arabic, and Chinese.[102-106] Furthermore, the existence and validation of these surveys across multiple languages facilitates clinical implementation globally. With these reliable instruments, we quantified the negative impact of cisplatin-related ototoxicity in TCS and risk-stratified patients for available interventions. Although the HHIA and TFPQ assess toxicity-specific impact, it should be recognized that cisplatin-treated TCS may have comorbidities.[42,43] The extent to which comorbidities might influence the perception of HL- or tinnitus-specific effects is unknown; however, in the general population, both HL and tinnitus typically affect older individuals with multiple comorbidities, and the HHIA and TPFQ have been extensively validated in these populations.[44,45,62,107,108] Moreover, each question is phrased to specifically query and isolate the impact of either HL or tinnitus per se on functional status. Although we found strong associations between worse HL or tinnitus and greater cognitive dysfunction using rigorous definitions (Appendix 1), we relied on self-report; thus, this finding requires confirmation in studies with additional objective measures. Some investigations with objective neurocognitive testing show that TCS have impaired cognitive function,[109-111] but others do not,[112] as recently reviewed.[43] Although response bias is a potential concern in any questionnaire study, we found no differences in survey completion rates on the basis of whether or not the patient had ototoxicity.

Ten-year TC survival rates now exceed 95%, given the effectiveness of cisplatin-based treatments[14]; thus, the high benefit-versus-risk ratio in using cisplatin to treat and cure TC, especially in young patients, is noteworthy. Accordingly, cisplatin should not be avoided, but attention must be turned to survivorship, including an awareness of the functional impact of ototoxicity. Routine follow-up of adult-onset cisplatin-treated ototoxicity in cancer survivors should begin with pre-chemotherapy baseline measurements, resume shortly after treatment, and include annual query for HL/tinnitus status and severity, especially as patients age, so that they are presented with available treatment strategies. For patients with HL or tinnitus, administration of the HHIA or TPFQ should be considered to accurately risk-stratify survivors for available interventions, as discussed above, with referral to audiologists and other specialists for treatments. Among TCS with HL here, approximately 1/3 reported mild/moderate or greater handicap on the HHIA overall score and would have been referred for audiologic evaluation and intervention in a general practice. Moreover, TCS with more than a mild clinical rating on the HHIA and TPFQ could be at higher risk for AHO, including cognitive dysfunction, fatigue, and poorer self-reported health. The potentially severe, negative impact of cisplatin-related ototoxicity on functional status warrants clinical intervention, survivorship support, and education.

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Patient-Reported Functional Impairment Due to Hearing Loss and Tinnitus After Cisplatin-Based Chemotherapy

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APPENDIX

APPENDIX 1. DEFINITIONS USED FOR ADVERSE HEALTH OUTCOMES AND OTHER VARIABLES

Hearing loss: Answered yes to any of the following questions: (1) a little, quite a bit, or very much for difficulty hearing[40]; (2) a little, quite a bit, or very much for reduced hearing[39]; (3) problems hearing words, sounds, or language in crowds; and (4) required a hearing aid.

Tinnitus: Answered a little, quite a bit, or very much for for ringing or buzzing your ears[39] or yes to ringing or buzzing in your ears.

Fatigue: Answered yes to "In the past 7 days, have you experienced any type of fatigue?" and had a T-score ≥ 55 on the Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form 6a.[41,50,53,54] Only participants who replied yes were administered the latter form.

Cognitive dysfunction: Answered yes to "Have you had any problems in your ability to think, concentrate, or remember items (ie, cognitive function) in the past 7 days?" and had a T-score ≤ 45 on the PROMIS Cognitive Function Abilities Short Form 4a.[48,55] Only participants who replied yes were administered the latter form.

Depression: Score ≥ 3 on the Two-Question Screening Survey for Depression[52] or reported the use of prescription medications for depression.

Anxiety: Reported the use of prescription medications for anxiety, or answered yes to "In the past 7 days, have you had any persistent fearfulness or worry (ie, anxiety)?" and had a T-score ≥ 55 on the PROMIS Anxiety Short Form 4.[41,49] Only participants who replied yes were administered the latter form.

Hypertension: Answered yes to "Have you ever been told by a doctor or other health care provider that you had one of the following conditions: (a) hypertension" or reported the use of prescription medications for hypertension.

Hypercholesterolemia: Answered yes to "Have you ever been told by a doctor or other health care provider that you had one of the following conditions: (b) high cholesterol" or reported the use of prescription medications for cholesterol.

Overall self-reported health: Possible responses of excellent, very good, good, fair, or poor to "In general, would you say your health is?" from the PROMIS 10-item Global Health v1.2.[51]

Noise exposure: Categorized as none, work-related only, non–work-related only, or both from the following questions: (1) "Have you ever had a job where you were exposed to loud noise for 5 or more hours a week? (Loud noise means noise so loud that you had to speak in a raised voice to be heard)"; (2) "Outside of a job, have you ever been exposed to steady loud noise or music for 5 or more hours a week? (This is noise so loud that you have to raise your voice to be heard. Examples are noise from power tools, lawn mowers, farm machinery, cars, trucks, motorcycles, or loud music)."

Physical activity: Exercise was assessed with a validated questionnaire[57,58] that asked participants to report their average time per week (over the past year) spent in each of nine recreational activities: walking or hiking (including walking to work); jogging (> 10 min/mile); running (≤ 10 min/mile); bicycling (including stationary bike); aerobic exercise/dance or exercise machines; lower-intensity exercise, yoga, stretching, or toning; tennis, squash, or racquetball; lap swimming; weight lifting or strength training; and other: please specify activity. Each physical activity was assigned a metabolic equivalent task (MET) value, which is a commonly used metric for describing the relative energy expenditure of a specific type of physical activity (1 MET = 1 kcal/kg/h or the energy cost of sitting quietly).[57,58] The physical activities were then grouped on the basis of the MET values into categories of vigorous (≥ 6 METs) and moderate (3 to < 6 METs) physical activities.[56]

Race: Categorized as White if responded only as White to "Do you identify yourself as being (check all that apply)"; categorized as other if responded as Black or African American, Asian, American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, other, please specify, or in any combination with or without White.

Education: Categorized as not college graduate if responded 1-8 years (grade school), 9-12 years (high school), but did not graduate, completed high school/General Educational Development, training after high school, other than college/university, or some college/university to "What is the highest grade or level of schooling that you have completed?"; categorized as college or postgraduate if responded college/university graduate or postgraduate level.

Marital Status: Categorized as married/living as married if responded married or living as married to "Which of these possibilities best describes your current marital status?"; categorized as not married if responded single or never married, divorced, widowed, or separated or no longer living as married.

APPENDIX 2. HEARING HANDICAP INVENTORY FOR ADULTS

The Hearing Handicap Inventory for Adults (HHIA) is a widely accepted measure in the field of audiology and otolaryngology. The questionnaire is highly reliable (test-retest; r = 0.97) with high internal consistency (Cronbach's α = .93).[61] In addition, Cronbach's α was calculated in our study, with scores of .95 and .94 for the emotional and social domains, respectively, and .97 overall. The HHIA has three response categories that are differently weighted (4, 2, 0), which are summed to a 0-100 total score. The questionnaire has items related to emotional (E) and social (S) domains. Patients were asked to complete the HHIA if they self-reported hearing loss (HL) as described in Appendix 1. Consistent with previous reports,[45,62] three degrees of severity ratings were applied: none/minimal, 0%-16%; mild/moderate, 17%-42%; and severe, 43%-100%.

Emotional (E) and social (S) domain scores are sums of the respective 13 and 12 items. Each item is scored either 4 (yes), 2 (sometimes), or 0 (no). The emotional domain has a possible score of 0-52. The social domain has a possible score of 0-48. If at least seven emotional items are answered, missing emotional items are mean-imputed. If at least six social items are answered, missing social items are mean-imputed. If < seven emotional items or six social items are answered, then the emotional domain score or social domain score is set to missing, respectively. Domain scores are rounded to the nearest whole number. Domain percent scores are percentages of the total possible domain score. The total score is the sum of the two domain scores. The total score is set to missing when either the emotional or social domain scores are missing.

Instructions: The Purpose of the Below Scale Is to Identify the Problems Your HL May Be Causing You
Check YES, SOMETIMES, or NO for Each Question. DO NOT Skip a Question If You Avoid a Situation Because of Your Hearing Problem. If You Use a Hearing Aid, Please Answer the Way You Hear WITHOUT Your Aid

		Yes (4)	Sometimes (2)	No (0)
S1	Does a hearing problem cause you to use the phone less often than you would like?			
E2	Does a hearing problem cause you to feel embarrassed when meeting new people?			
S3	Does a hearing problem cause you to avoid groups of people?			
E4	Does a hearing problem make you irritable?			
E5	Does a hearing problem cause you to feel frustrated when talking to members of your family?			
S6	Does a hearing problem cause you difficulty when attending a party?			
S7	Does a hearing problem cause you difficulty hearing/ understanding coworkers, clients, or customers?			
S8	Do you feel handicapped by a hearing problem?			
S9	Does a hearing problem cause you difficulty when visiting friends, relatives, or neighbors?			
E10	Does a hearing problem cause you to feel frustrated when talking to coworkers, clients, or customers?			
S11	Does a hearing problem cause you difficulty in the movies or theater?			
E12	Does a hearing problem cause you to be nervous?			
S13	Does a hearing problem cause you to visit friends, relatives, or neighbors less often than you would like?			
E14	Does a hearing problem cause you to have arguments with family members?			
S15	Does a hearing problem cause you difficulty when listening to TV or radio?			
S16	Does a hearing problem cause you to go shopping less often than you would like?			
E17	Does any problem or difficulty with your hearing upset you at all			
E18	Does a hearing problem cause you to want to be by yourself?			
S19	Does a hearing problem cause you to talk to family members less often than you would like?			
E20	Do you feel that any difficulty with your hearing limits or hampers your personal or social life?			
S21	Does a hearing problem cause you difficulty when in a restaurant with relatives or friends?			
E22	Does a hearing problem cause you to feel depressed?			
S23	Does a hearing problem cause you to listen to TV or the radio less often than you would like?			
E24	Does a hearing problem cause you to feel uncomfortable when talking to friends?			
E25	Does a hearing problem cause you to feel left out when you are with a group of people?			

APPENDIX 3. TINNITUS PRIMARY FUNCTION QUESTIONNAIRE

The Tinnitus Primary Function Questionnaire[44] is a 20-item self-assessment quantifying the impact of tinnitus per se on four functional domains: concentration (C), emotion (E), hearing (H), and sleep (S). The questionnaire is highly reliable with high construct validity ($r = 0.77$) and high internal consistency (Cronbach's $\alpha = .92$).[44] In addition, Cronbach's α was calculated in our study for all four subscales: concentration (.880), emotion (.84), hearing (.81), and sleep (.94). Patients were asked to complete the Tinnitus Primary Function Questionnaire if they self-reported 'tinnitus' through two questions as described in Appendix 1. Similar to prior reports and uses,[63,64] and for consistency with the Hearing Handicap Inventory for Adults categorization, three categories of severity are used: none/minimal, 0%-16%; mild/moderate, 17%-42%; and severe, 43%-100%.

Concentration (C), emotion (E), hearing (H), and sleep (S) domain scores are the means of the respective five domain items. Each item has a possible score of 0-100. If at least three items are answered from a respective domain, the missing domain items are mean-imputed. If less than three items are answered from a respective domain, then the respective domain score is set to missing. The total score is the mean of the nonmissing domain scores. The total score is set to missing when < 10 total items are answered.

APPENDIX 4. SUPPLEMENTAL METHODS

The Supplemental Methods provide additional detail to the Patients and Methods section in the manuscript.

Study Population

The Platinum Study enrolled testicular cancer survivors (TCS) from eight cancer centers in the United States, Canada, and Great Britain (2012-2018), as described in detail elsewhere.[3,42,43] Eligible participants were age at least 18 years at consent and $\leq$ 60 years at diagnosis, had a serologically or histologically confirmed germ cell tumor, and were treated with cisplatin-based chemotherapy. Patients were well characterized in terms of diagnostic and treatment information abstracted from medical records, including cumulative cisplatin dose. We included all patients with complete surveys as of the cutoff date for this report (February 24, 2022): this comprised 243 TCS (66%) of 371 TCS who consented to participate. To evaluate whether patients with hearing loss (HL) or tinnitus were more likely to fill out the questionnaire (eg, response bias), we determined how many of the 371 patients had reported HL/tinnitus at prior audiometric examination. Of the 371 patients, 175 (47%) had reported HL and 164 (69%) reported tinnitus; of these patients, 122/175 (69%) with HL and 113/164 (69%) with tinnitus completed the survey. Of the 371 patients, 196 (53%) had not reported HL at the time of prior audiometric examination, with 121/196 (62%) completing the survey; and 207 did not report tinnitus

Instructions: Please Indicate Your Agreement With Each Statement on a Scale From 0 (completely disagree) to 100 (completely agree)

		0-100
C1	When there are lots of things happening at once, my tinnitus interferes with my ability to attend to the most important thing	
C2	I feel like my tinnitus makes it difficult for me to concentrate on some tasks	
C3	I have difficulty focusing my attention on some important tasks because of tinnitus	
C4	My inability to think about something undisturbed is one of the worst effects of my tinnitus	
C5	I have trouble concentrating while I am reading in a quiet room because of tinnitus	
E6	My tinnitus is annoying	
E7	My emotional peace is one of the worst effects of my tinnitus	
E8	I am depressed because of my tinnitus	
E9	I am anxious because of my tinnitus	
E10	I just wish my tinnitus would go away. It is so frustrating	
H11	My tinnitus masks some speech sounds	
H12	The effects of tinnitus on my hearing are worse than the effects of my HL	
H13	My tinnitus, not my HL, interferes with my appreciation of music and songs	
H14	In addition to my HL, my tinnitus interferes with my understanding of speech	
H15	One of the worst things about my tinnitus is its effect on my speech understanding, over and above any effect of my HL	
S16	I have difficulty getting to sleep at night because of my tinnitus	
S17	The difficulty I have sleeping is one of the worst effects of my tinnitus	
S18	I am tired during the day because my tinnitus has disrupted my sleep	
S19	I lie awake at night because of my tinnitus	
S20	When I wake up in the night, my tinnitus makes it difficult to get back to sleep	

at the time of prior audiometric examination, with 130/207 (63%) completing the survey. There were no statistically significant differences in questionnaire completion between those with and without HL ($P = .11$) or those with and without tinnitus ($P = .21$). See Appendix 1 for additional details on questions and scoring criteria.

Audiometric Testing

At initial enrollment, participants also underwent extensive audiologic testing.[3,42,43,46,47] Air-conduction audiometric thresholds for left and right ears were measured at each of 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, and 12k Hz.[3,46] The geometric mean of the air-conduction audiometric thresholds of left and right ears at the five upper frequencies that were evaluated (4, 6, 8, 10, and 12k Hz) was used to define an aggregate measure.[3,46] For each patient, the extent of HL using this aggregate measure was determined by applying criteria of the American Speech-Language- Hearing Association (ASHA),[47] which defines hearing in decibels referenced to hearing level (dB-HL; Frank T: American Journal of Audiology 6:29-32, 1997) as normal (< 15), slight (16-25), mild (26-40), moderate (41-55), moderately severe (56-70), severe (71-90), or profound HL (> 90).

Identifying Patients With HL and Tinnitus: Effect of Severity of HL or Tinnitus on Patient-Reported Functional Status

The 137 patients who met criteria for HL as defined in Appendix 1 were also asked to complete a questionnaire (the Hearing Handicap Inventory for Adults [HHIA])[45,59-62] that was designed for patients with HL and validated in patients with HL. The HHIA asks patients with HL 25 questions about the handicap imposed by HL in two functional domains: social and emotional (Appendix 2).[45] If participants reported using hearing aids (a small minority in the present investigation), they were instructed to answer questions with respect to their functionality without hearing aids. The characteristics and functional impairment measured with the HHIA stratified by the severity of HL according to the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy 20-Item Scale are shown in Table 2.

The 147 patients who met criteria for tinnitus as defined in Appendix 1 were also asked to complete a questionnaire (the Tinnitus Primary Function Questionnaire [TPFQ]) designed for patients with tinnitus and validated in patients with tinnitus. The TPFQ asks patients with tinnitus 20 questions about the handicap imposed by their tinnitus in four functional domains: concentration, emotion, hearing, and sleep (Appendix 3). Of the 147 patients identified with tinnitus, three patients had insufficient data across the four subdomains to estimate the total handicap; thus, reported frequencies are based on 144 patients. The characteristics and functional impairment measured with the TPFQ stratified by the severity of tinnitus according to the Scale for Chemotherapy-Induced Long-Term Neurotoxicity are shown in Table 3.

Measurement of Adverse Health Outcomes

For all 243 TCS in the study, data with regard to patient-reported adverse health outcomes (AHOs) that were defined a priori (ie, cognitive dysfunction, anxiety, depression, fatigue, and overall health) were collected with validated instruments including those from the National Institutes of Health–derived Patient-Reported Outcomes Measurement Information System (Andersen BL et al: J Clin Oncol 32: 1605-1619, 2014).[41,48-52] Each question and its scoring criteria are shown in Appendix 1. The results for the 243 TCS are shown in Table 4 stratified by the patient's response to the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy 20-Item Scale with regard to HL and by his response to the Scale for Chemotherapy-Induced Long-Term Neurotoxicity with regard to tinnitus.

For the subgroup of 137 TCS who met criteria for HL and were thus administered the HHIA, we also evaluated the effect of HHIA category (ie, none/minimal, mild/moderate, and severe handicap) on the five prespecified patient-reported AHOs. The results for the 136 (99%) patients who completed the HHIA are shown in the upper half of Table 5.

For the subgroup of 147 TCS who met criteria for tinnitus and were thus administered the TPFQ, we also evaluated the effect of TPFQ category (ie, none/minimal, mild/moderate, and severe handicap) on these five patient-reported AHOs. The results for the 144 (98%) TCS with tinnitus who completed the entire TPFQ are shown in the bottom half of Table 5.

Statistical Analyses

As noted above, questions and scoring of all study end points are detailed in Appendices 1, 2, and 3. We also calculated the internal reliability of the HHIA and TPFQ with Cronbach alphas for this study, with the results shown in Appendices 2 and 3.