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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

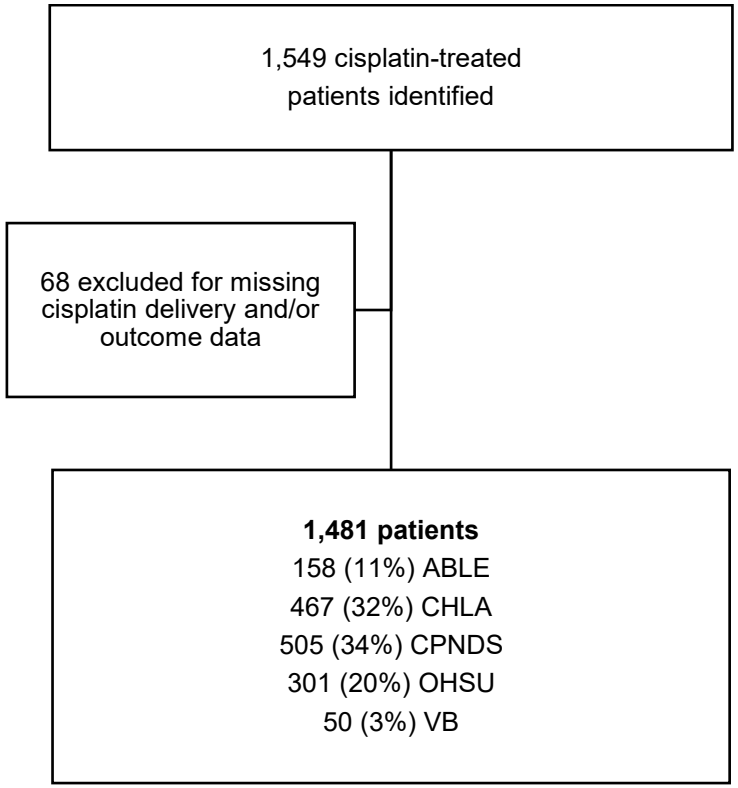
Supplement to: Moke DJ, Luo C, Millstein J, et al. Prevalence and risk factors for cisplatin-induced hearing loss in children, adolescents, and young adults: a multi-institutional North American cohort study. *Lancet Child Adolesc Health* 2021; published online Feb 11. http://dx.doi.org/10.1016/S2352-4642(21)00020-1.

Supplementary Material Table of Context

Figure S1: Patient data included for each endpoint

Diagram indicating sources of (A) patient data and (B) inclusion for each study endpoint. Cisplatin-treated patients identified from treatment records except in the Vanderbilt cohort where patients were identified through a survivorship clinic. Survival analyses therefore excluded patients from the Vanderbilt cohort to reduce risk of bias favoring survival. Hearing loss endpoints included all patients with audiology assessments passing central review at last follow-up and end of therapy. ABLE= Applying Biomarkers to Minimize Long-Term Effects of Childhood/Adolescent Cancer Treatment; CHLA= Children's Hospital Los Angeles; CPNDS= Canadian Pharmacogenomics Network for Drug Safety; OHSU=Oregon Health & Science University Pediatric Hospital; VB=Vanderbilt Reach for Cancer Survivorship Program.

A



B

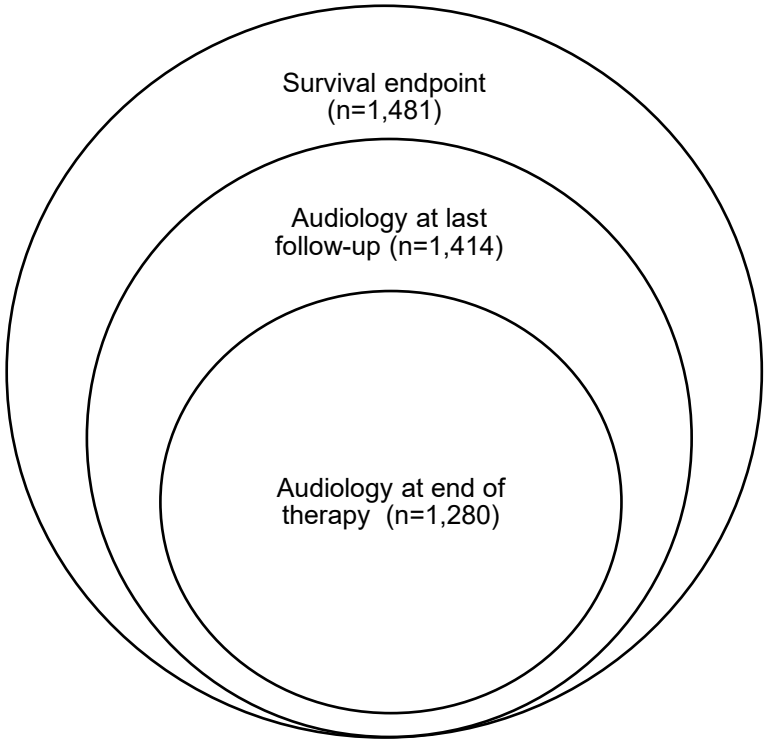


Table S1: International Society of Pediatric Oncology Boston (SIOP) grading Scale*

SIOP Grade	Threshold	Frequencies*	Audiology Recommendation
0	≤ 20 dB	All tested frequencies	No intervention
1	> 20 dB	At greater than 4000 Hz (6,000 or 8,000 Hz)	FM device, preferential classroom seating, or other communication aid, educational support
2	> 20 dB	At 4000 Hz and above	Hearing aid or cochlear implant, educational support
3	> 20 dB	At 2000 Hz or 3000 Hz and above	
4	> 40 dB	At 2000 Hz and above	

*Included frequencies 2,000 Hz through 8,000 Hz. dB= decibel; Hz=hertz; *Adapted from Brock et. al., J Clin Oncol; 30(19):2012*

Table S2: Multivariable model for risk of hearing aid recommendation at latest follow-up

Variables	N	Multivariable Model[2]	
		aOR[1] [95%CI]	p-value
Vincristine exposure			
No	557	Ref	
Yes	21	2·01 [1·10, 3·74]	0·025
Unknown	680	0·97 [0·22, 3·54]	0·96
CRT dose, Gy			
0	931	Ref	
>0 to ≤ 50	55	1·80 [0·78, 4·04]	0·16
>50	272	1·92 [1·08, 3·45]	0·028
VP shunt			
No	627	Ref	
Yes	515	1·61 [0·97, 2·67]	0·067
Unknown	116	0·65 [0·43, 0·99]	0·046
Stem cell transplant			
No	991	Ref	
Yes	256	1·63 [1·03, 2·57]	0·037
Unknown	11	1·60 [0·40, 6·15]	0·49
Carboplatin exposure			
No	614	Ref	
Yes	437	1·99 [1·27, 3·10]	0·0025
Unknown	207	0·78 [0·49, 1·22]	0·28
Cisplatin dosing parameters			
Cisplatin total cumulative dose, +100 mg/m^2	1258	1·05 [0·94, 1·17]	0·40
Cisplatin prescribed cycle dose, +50 mg/m^2/cycle	1258	1·93 [1·30, 2·96]	0·0017
Cisplatin prescribed daily dose, +10 mg/m^2/day	1258	1·09 [1·00, 1·17]	0·040

[1]aOR = adjusted Odds Ratio: multivariable logistic regression model includes independent variables as depicted and additionally adjusted for sex, age at diagnosis, race, ethnicity, and underlying malignancy (central nervous system, germ cell tumor, hepatoblastoma or hepatocellular carcinoma, neuroblastoma, osteosarcoma, other). Cisplatin dosing parameters were evaluated in a series of nested logistic regression models including progressively more granular dosing (Model 2: +cumulative dose; Model 3: +cumulative dose, cycle dose; Model 4: +cumulative dose, cycle dose, daily dose; Model 5: +cumulative dose, cycle dose, daily dose, dose rate); Likelihood Ratio Tests compared each model (Base Model vs. Model 2, p= 0·56; Models 2 vs. 3, p= 0·0010; Models 3 vs. 4, p= 0·043; Models 4 vs. 5, p= 0·46). Dosing rate was not significant; Model 4 reported.

Table S3: Risk factors for moderate/severe hearing loss at latest follow-up in patients stratified by receipt of cranial radiation therapy

Variables	With cranial radiotherapy					Without cranial radiotherapy				
	N	Univariable model		Multivariable model[2]		N	Univariable model		Multivariable model[2]	
		OR [95%CI]	p-value	aOR[1] [95%CI]	p-value		OR [95%CI]	p-value	aOR[1] [95%CI]	p-value
Stem cell transplant										
No	243	Ref		Ref		639	Ref		Ref	
Yes	60	1·83 [1·03, 3·32]	0·042	1·15 [0·52, 2·54]	0·73	186	3·17 [2·26, 4·50]	<0·0001	0·79 [0·42, 1·46]	0·45
Unknown	35	0·71 [0·34, 1·44]	0·34	2·77 [0·83, 9·67]	0·10	98	1·19 [0·77, 1·83]	0·43	1·91 [0·84, 4·35]	0·12
Carboplatin exposure										
No	163	Ref		Ref		403	Ref		Ref	
Yes	44	1·69 [0·85, 3·46]	0·14	1·47 [0·61, 3·73]	0·40	155	4·68 [3·14, 7·09]	<0·0001	2·81 [1·57, 5·08]	0·00054
Unknown	131	0·61 [0·38, 0·97]	0·039	0·40 [0·17, 0·91]	0·033	365	1·36 [1·02, 1·82]	0·039	1·11 [0·62, 1·97]	0·73
Vincristine exposure										
No	46	Ref		Ref		520	Ref		Ref	
Yes	289	4·34 [2·15, 9·55]	<0·0004	4·58 [1·43, 16·63]	0·014	390	5·77 [4·34, 7·71]	<0·0001	3·36 [1·86, 6·17]	<0·0001
Unknown	3	7·2 [0·63, 164·65]	0·12	5·77 [0·32, 188·37]	0·25	13	2·3 [0·73, 7·05]	0·14	2·85 [0·71, 11·66]	0·14
VP shunt										
No	116	Ref		Ref		401	Ref		Ref	
Yes	72	2·31 [1·27, 4·25]	0·0065	2·30 [1·16, 4·66]	0·018	32	3·05 [1·44, 6·89]	0·0047	1·28 [0·45, 3·77]	0·65
Unknown	150	1·63 [1·00, 2·68]	0·050	2·14 [0·98, 4·75]	0·058	490	1·16 [0·89, 1·51]	0·28	1·07 [0·63, 1·81]	0·80
Time from diagnosis to audiogram, years	338	1·16 [1·08, 1·24]	<0·0001	1·18 [1·08, 1·30]	0·00025	923	1·09 [1·05, 1·12]	<0·0001	1·11 [1·06, 1·16]	<0·0001
Cisplatin dosing parameters										
Cisplatin total cumulative dose, +100 mg/m^2	338	0·96 [0·80, 1·14]	0·62	0·92 [0·73, 1·17]	0·51	923	1·13 [1·03, 1·23]	0·0075	1·28 [1·14, 1·44]	<0·0001
Cisplatin prescribed cycle dose, +50 mg/m^2/cycle	338	1·99 [1·08, 3·90]	0·035	0·86 [0·27, 2·53]	0·79	923	1·64 [1·40, 1·94]	<0·0001	2·88 [1·58, 5·49]	0·00086
Cisplatin prescribed daily dose, +10 mg/m^2/day	338	1·31 [1·15, 1·50]	<0·0001	1·36 [1·12, 1·70]	0·0029	923	1·17 [1·12, 1·22]	<0·0001	1·20 [1·08, 1·35]	0·0011
Cisplatin dose rate, +1 mg/m^2/hour	338	1·03 [1·00, 1·08]	0·14	1·03 [0·98, 1·11]	0·30	923	1·02 [1·01, 1·03]	<0·0001	0·96 [0·93, 0·99]	0·019

[1]aOR = adjusted Odds Ratio: multivariable logistic regression models include independent variables as depicted and additionally adjusted for sex, age at diagnosis, race, ethnicity, and underlying malignancy (central nervous system, germ cell tumor, hepatoblastoma or hepatocellular carcinoma, neuroblastoma, osteosarcoma, other). [2]Cisplatin dosing parameters were evaluated in a series of nested logistic regression models including progressively more granular dosing (Model 2: +cumulative dose; Model 3: +cumulative dose, cycle dose; Model 4: +cumulative dose, cycle dose, daily dose; Model 5: +cumulative dose, cycle dose, daily dose, dose rate). Likelihood Ratio Tests compared models in patient receiving cranial radiotherapy (Base Model vs. Model 2, p= 0·36; Models 2 vs. 3, p= 0·55; Models 3 vs. 4, p= 0·0020; Models 4 vs. 5, p= 0·25) and in those without (Base Model vs. Model 2, p<0·0001; Models 2 vs. 3, p= 0·0081; Models 3 vs. 4, p= 0·018; Models 4 vs. 5, p= 0·013). Model 5 reported for both groups.

Table S4: Risk factors for moderate/severe hearing loss at latest follow-up stratified by underlying CNS malignancy

Variables	CNS malignancy					Without CNS malignancy				
	N	Univariable model		Multivariable model[2]		N	Univariable model		Multivariable model[2]	
		OR [95%CI]	p-value	aOR[1][95%CI]	p-value		OR [95%CI]	p-value	aOR[1] [95%CI]	p-value
Stem cell transplant										
No	243	Ref		Ref		639	Ref		Ref	
Yes	103	1·77 [1·11, 2·86]	0·018	1·18 [0·57, 2·42]	0·64	143	3·33 [2·28, 4·92]	<0·0001	0·88 [0·45, 1·68]	0·70
Unknown	49	0·68 [0·36, 1·27]	0·23	1·75 [0·56, 5·55]	0·34	84	1·22 [0·77, 1·93]	0·39	2·08 [0·90, 4·81]	0·086
Carboplatin exposure										
No	156	Ref		Ref		410	Ref		Ref	
Yes	65	1·57 [0·87, 2·88]	0·14	1·28 [0·59, 2·84]	0·54	134	5·06 [3·30, 7·90]	<0·0001	2·98 [1·63, 5·55]	0·00046
Unknown	174	0·76 [0·49, 1·18]	0·22	0·55 [0·25, 1·19]	0·13	322	1·20 [0·89, 1·62]	0·24	0·89 [0·49, 1·60]	0·69
Vincristine exposure										
No	41	Ref		Ref		525	Ref		Ref	
Yes	347	4·56 [2·20, 10·42]	0·00011	2·75 [1·00, 8·04]	0·055	332	6·00 [4·45, 8·14]	<0·0001	2·83 [1·78, 4·53]	<0·0001
Unknown	7	4·74 [0·89, 28·07]	0·068	2·52 [0·35, 19·62]	0·36	9	2·16 [0·53, 8·26]	0·26	1·47 [0·31, 6·90]	0·61
CRT dose, Gy										
0	82	Ref		Ref		841	Ref		Ref	
>0 to ≤ 50	41	0·41 [0·19, 0·88]	0·023	0·55 [0·19, 1·65]	0·29	12	2·63 [0·82, 9·93]	0·12	2·46 [0·52, 12·31]	0·26
>50	272	0·70 [0·42, 1·15]	0·16	0·83 [0·41, 1·69]	0·61	13	0·59 [0·16, 1·81]	0·38	1·04 [0·23, 3·77]	0·96
VP shunt										
No	127	Ref		Ref		390	Ref		Ref	
Yes	103	2·49 [1·47, 4·28]	0·00083	2·40 [1·31, 4·44]	0·0048	1	-	-	-	-
Unknown	165	1·64 [1·03, 2·62]	0·039	2·63 [1·24, 5·71]	0·013	475	1·14 [0·87, 1·50]	0·33	0·89 [0·52, 1·50]	0·65
Time from diagnosis to audiogram, years	395	1·16 [1·09, 1·24]	<0·0001	1·20 [1·11, 1·31]	<0·0001	866	1·08 [1·05, 1·12]	<0·0001	1·08 [1·04, 1·13]	0·00037
Cisplatin dosing parameters										
Cisplatin total cumulative dose, +100 mg/m^2	395	0·96 [0·80, 1·14]	0·62	0·91 [0·73, 1·12]	0·37	866	1·17 [1·07, 1·29]	0·0004	1·30 [1·15, 1·46]	<0·0001
Cisplatin prescribed cycle dose, +50 mg/m^2/cycle	395	2·57 [1·34, 5·03]	0·0052	0·60 [0·14, 1·88]	0·41	866	1·77 [1·50, 2·09]	<0·0001	2·71 [1·74, 4·32]	<0·0001
Cisplatin prescribed daily dose, +10 mg/m^2/day	395	1·38 [1·22, 1·56]	<0·0001	1·42 [1·16, 1·85]	0·0021	866	1·15 [1·10, 1·21]	<0·0001	1·20 [1·12, 1·29]	<0·0001
Cisplatin dose rate, +1 mg/m^2/hour	395	1·02 [0·98, 1·08]	0·34	1·01 [0·96, 1·08]	0·67	866	1·03 [1·02, 1·04]	<0·0001	0·97 [0·95, 0·99]	0·0019

[1] aOR = adjusted Odds Ratio: multivariable logistic regression models include independent variables as depicted and additionally adjusted for sex, age at diagnosis, race, ethnicity, and underlying malignancy (central nervous system, germ cell tumor, hepatoblastoma or hepatocellular carcinoma, neuroblastoma, osteosarcoma, other). [2]Cisplatin dosing parameters were evaluated in a series of nested logistic regression models including progressively more granular dosing (Model 2: +cumulative dose; Model 3: +cumulative dose, cycle dose; Model 4: +cumulative dose, cycle dose, daily dose; Model 5: +cumulative dose, cycle dose, daily dose, dose rate). Likelihood Ratio Tests compared models in patients with CNS tumors (Base Model vs. Model 2, p= 0·25; Models 2 vs. 3, p= 0·53; Models 3 vs. 4, p= 0·00058; Models 4 vs. 5, p= 0·66) and in those without (Base Model vs. Model 2, p<0·0001; Models 2 vs. 3, p= 0·014; Models 3 vs. 4, p<0·0001; Models 4 vs. 5, p= 0·0013). Model 5 reported for both groups. CNS = central nervous system tumor; CRT = cranial radiotherapy; VP shunt – ventriculoperitoneal (or other ventricular) shunt.

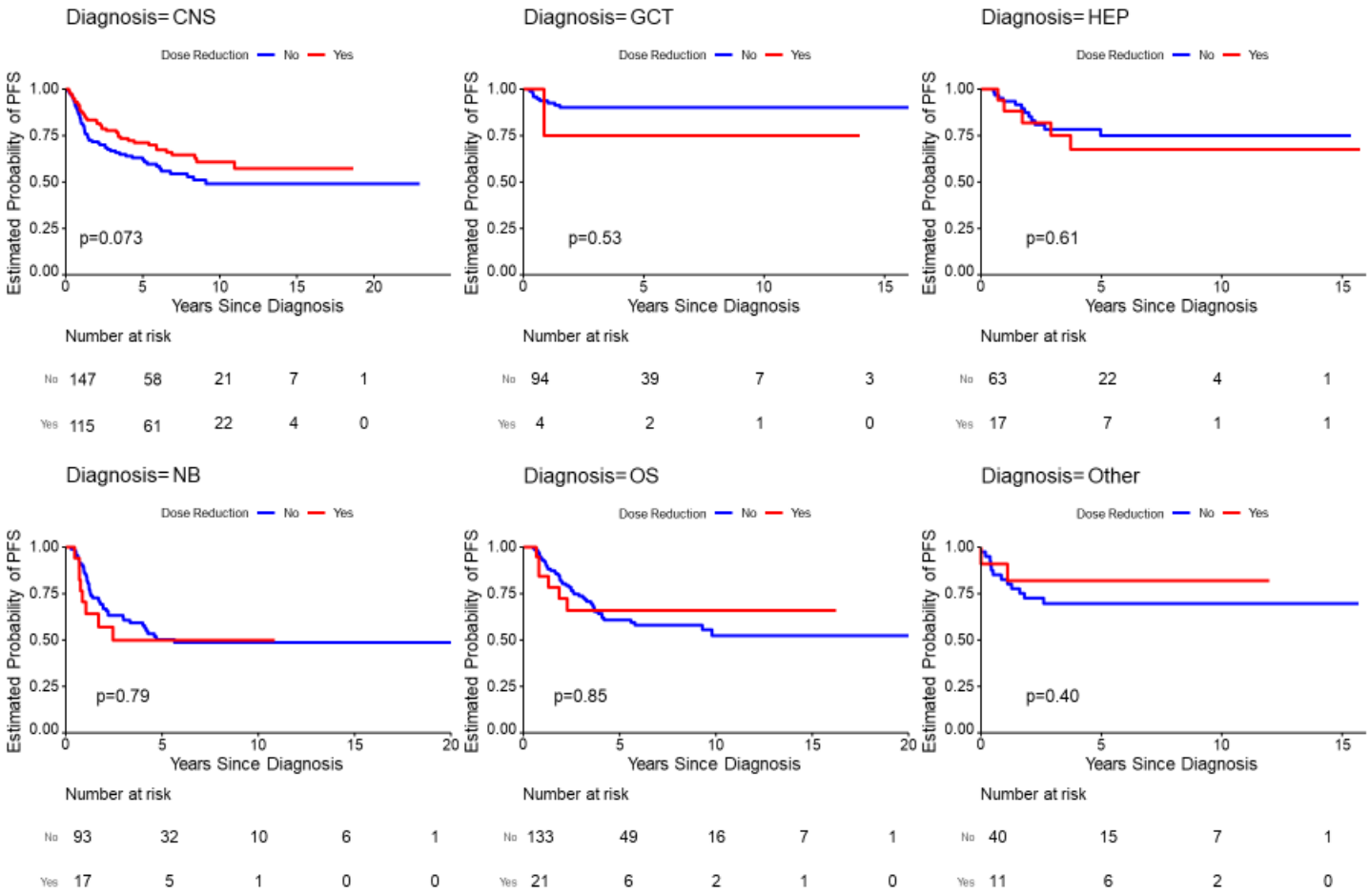
Table S5: Multivariable models for documented cisplatin dose reduction and progression-free and overall survival

Variables	Progression Free Survival					Overall Survival				
	N	Univariable Cox model		Multivariable Cox model[1]		N	Univariable Cox model		Multivariable Cox model[1]	
		HR [95%CI]	p-value	HR [95%CI]	p-value		HR [95%CI]	p-value	HR [95%CI]	p-value
Sex										
Female	300	Ref		Ref		301	Ref		Ref	
Male	455	1·09 [0·85, 1·42]	0·49	1·08 [0·83, 1·41]	0·57	456	1·27 [0·94, 1·71]	0·12	1·23 [0·90, 1·68]	0·19
Age at diagnosis, years										
<5	305	Ref		Ref		305	Ref		Ref	
5 to <15	302	0·87 [0·66, 1·15]	0·33	0·98 [0·68, 1·42]	0·91	303	0·86 [0·63, 1·17]	0·35	1·07 [0·71, 1·61]	0·75
≥15	148	0·73 [0·51, 1·06]	0·10	0·98 [0·60, 1·61]	0·94	149	0·69 [0·44, 1·06]	0·089	1·01 [0·57, 1·78]	0·98
Ethnicity										
Non-Hispanic	446	Ref				448	Ref			
Hispanic	293	1·11 [0·86, 1·43]	0·43	0·97 [0·68, 1·39]	0·88	293	0·89 [0·66, 1·20]	0·45	0·90 [0·58, 1·38]	0·62
Unknown	16	0·52 [0·13, 2·11]	0·36	0·73 [0·16, 3·29]	0·68	16				
Race										
White	478	Ref		Ref		480	Ref		Ref	
Black	26	1·44 [0·76, 2·74]	0·26	1·52 [0·75, 3·08]	0·25	26	1·58 [0·80, 3·11]	0·18	2·00 [0·91, 4·39]	0·084
Asian	60	1·30 [0·81, 2·07]	0·28	1·45 [0·85, 2·48]	0·17	60	0·78 [0·41, 1·48]	0·45	1·25 [0·62, 2·52]	0·53
Other/unknown	191	1·21 [0·90, 1·62]	0·20	1·74 [1·17, 2·60]	0·0067	191	1·17 [0·84, 1·62]	0·36	3·10 [1·91, 5·04]	<0·0001
Diagnosis										
CNS	262	Ref				263	Ref			
Non-CNS	493	0·81 [0·63, 1·05]	0·11			494	0·71 [0·54, 0·95]	0·022		
Underlying malignancy[2]										
CNS	262	Ref				263	Ref			
Germ cell tumor	98	0·28 [0·14, 0·53]	0·00011			98	0·07 [0·02, 0·28]	0·00017		
Hepatic tumor (HB or HCC)	80	0·59 [0·35, 0·98]	0·042			80	0·34 [0·16, 0·70]	0·0035		
Neuroblastoma	110	1·35 [0·97, 1·90]	0·080			110	1·39 [0·97, 2·01]	0·076		
Osteosarcoma	154	0·94 [0·67, 1·31]	0·71			155	0·89 [0·61, 1·29]	0·55		
Other	51	0·73 [0·42, 1·28]	0·27			51	0·61 [0·32, 1·18]	0·14		
Stem cell transplant[3]										
No	576	Ref		Ref		578	Ref		Ref	
Yes	179	1·65 [1·27, 2·16]	0·00022	0·78 [0·49, 1·24]	0·29	179	1·49 [1·10, 2·02]	0·011	0·48 [0·29, 0·78]	0·0035
Carboplatin exposure[3]										
No	222	Ref		Ref		223	Ref		Ref	
Yes	79	2·31 [1·56, 3·42]	<0·0001	2·11 [1·27, 3·50]	0·0038	80	2·06 [1·38, 3·07]	0·00041	1·71 [1·01, 2·93]	0·048
Unknown	454	1·49 [1·10, 2·01]	0·010	1·32 [0·87, 1·99]	0·19	454	0·88 [0·63, 1·22]	0·44	0·57 [0·35, 0·94]	0·027
Vincristine exposure[3]										
No	285	Ref		Ref		286	Ref		Ref	
Yes	449	1·27 [0·96, 1·67]	0·088	0·61 [0·30, 1·23]	0·17	450	1·57 [1·14, 2·18]	0·0061	0·88 [0·36, 2·16]	0·78
Unknown	21	3·63 [2·05, 6·43]	<0·0001	1·91 [0·83, 4·40]	0·13	21	2·69 [1·28, 5·67]	0·0093	1·98 [0·67, 5·82]	0·22
CRT dose, Gy[3]										
0	542	Ref		Ref		543	Ref		Ref	
>0 to ≤ 50	12	1·11 [0·45, 2·70]	0·82	0·99 [0·36, 2·72]	0·98	13	1·56 [0·69, 3·55]	0·29	0·86 [0·33, 2·28]	0·77
>50	201	1·03 [0·78, 1·36]	0·84	0·95 [0·57, 1·60]	0·86	201	1·08 [0·79, 1·48]	0·63	0·63 [0·35, 1·14]	0·13

VP Shunt										
No	636	Ref		Ref		638	Ref		Ref	
Yes	115	1·53 [1·13, 2·08]	0·0066	1·48 [0·98, 2·22]	0·062	115	1·48 [1·04, 2·09]	0·028	1·33 [0·85, 2·06]	0·21
Unknown	4	0·61 [0·09, 4·37]	0·62	0·69 [0·08, 5·83]	0·74	4				
Cisplatin dosing parameters										
Cisplatin total cumulative dose, +100 mg/m^2	755	0·87 [0·79, 0·97]	0·011	0·92 [0·80, 1·05]	0·21	757	0·80 [0·71, 0·90]	0·00028	0·82 [0·70, 0·96]	0·013
Cisplatin prescribed cycle dose, +50 mg/m^2/cycle	755	1·32 [1·14, 1·52]	0·00019	1·95 [1·15, 3·30]	0·013	757	1·40 [1·19, 1·64]	<0·0001	2·75 [1·50, 5·04]	0·0011
Cisplatin prescribed daily dose, +10 mg/m^2/day	755	1·02 [0·98, 1·07]	0·34	0·93 [0·86, 1·01]	0·095	757	1·04 [0·99, 1·09]	0·12	0·98 [0·89, 1·08]	0·68
Cisplatin dose rate, +1 mg/m^2/hour	755	1·01 [1·00, 1·02]	0·019	0·99 [0·97, 1·01]	0·22	757	1·01 [1·001, 1·02]	0·031	0·98 [0·96, 1·01]	0·056
Cisplatin dose reduction										
No	570	Ref		Ref		571	Ref		Ref	
Yes	185	0·95 [0·71, 1·27]	0·73	0·86 [0·61, 1·21]	0·38	186	1·03 [0·74, 1·42]	0·87	0·83 [0·56, 1·23]	0·36

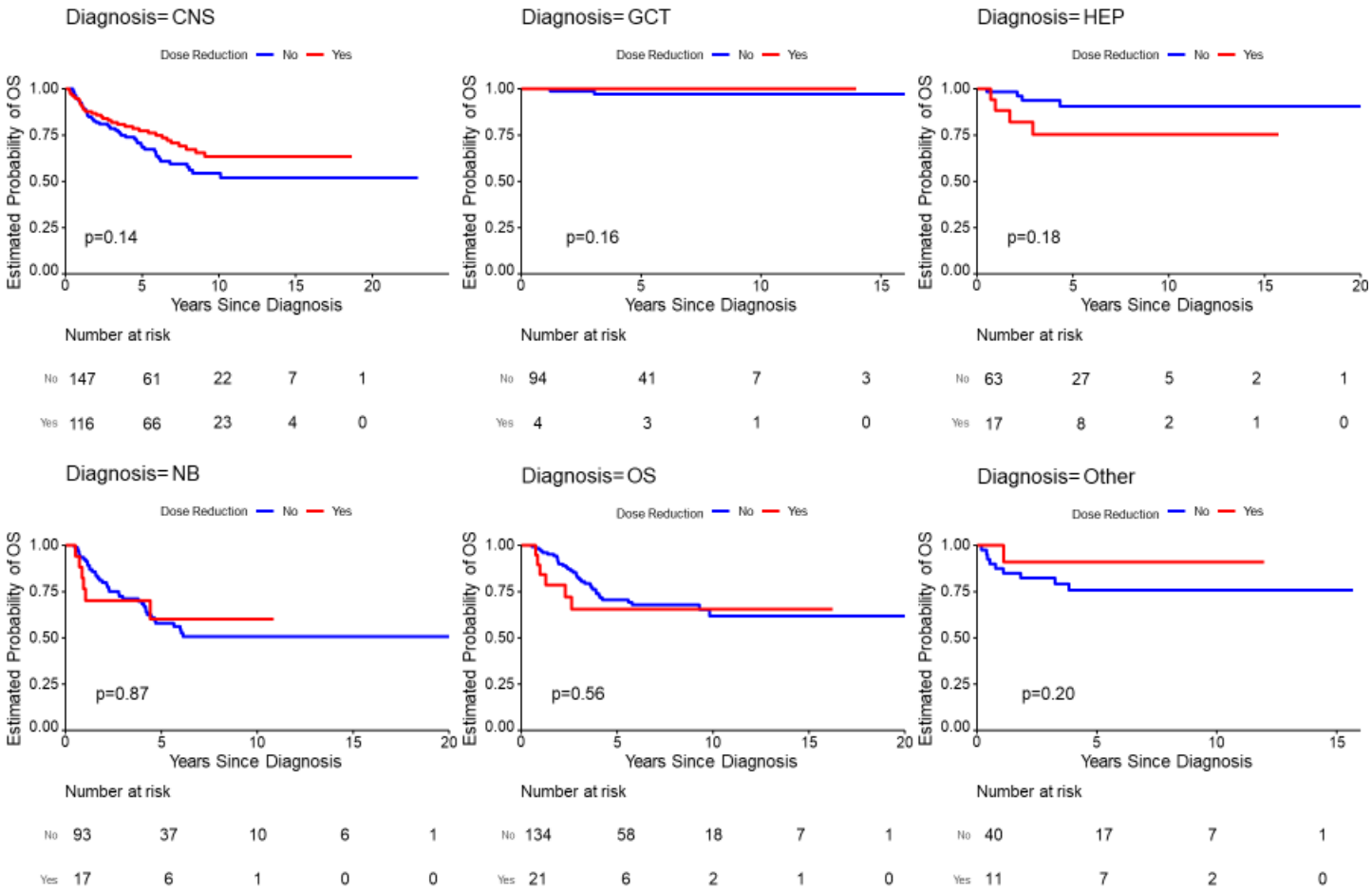
[1]Cisplatin dosing parameters were evaluated in a series of nested cox regression models including progressively more granular dosing (Model 2: +cumulative dose; Model 3: +cumulative dose, cycle dose; Model 4: +cumulative dose, cycle dose, daily dose; Model 5: +cumulative dose, cycle dose, daily dose, dose rate; Model 6: +cumulative dose, cycle dose, daily dose, dose rate, cisplatin dose reduction); Likelihood Ratio Tests compared each model for progression-free survival (Base Model vs. Model 2, p= 0·45; Models 2 vs. 3, p= 0·026; Models 3 vs. 4, p= 0·043; Models 4 vs. 5, p= 0·20; Models 5 vs. 6, p= 0·38) and overall survival (Base Model vs. Model 2, p= 0·041; Models 2 vs. 3, p= 0·0025; Models 3 vs. 4, p= 0·37; Models 4 vs. 5, p= 0·051; Models 5 vs. 6, p= 0·35). Model 6 showing variable of interest reported. [2]Underlying malignancy was modeled as a strata factor in multivariable cox models. [3]Treatment variables included to additionally account for regimen differences potentially affecting survival within diagnosis strata. CNS = central nervous system tumor; HB or HCC = hepatoblastoma or hepatocellular carcinoma; CRT = cranial radiotherapy; VP shunt – ventriculoperitoneal (or other ventricular) shunt.

Figure S2: Progression-free survival by cisplatin dose reduction stratified by underlying diagnosis



CNS=central nervous system tumor; GCT=germ cell tumor; HEP=hepatoblastoma or hepatocellular carcinoma; NB=neuroblastoma; OS=osteosarcoma.

Figure S3: Overall survival by cisplatin dose reduction stratified by underlying diagnosis



CNS=central nervous system tumor; GCT=germ cell tumor; HEP=hepatoblastoma or hepatocellular carcinoma; NB=neuroblastoma; OS=osteosarcoma.

Table S6: Multivariable models for cisplatin dosing and progression-free and overall survival

Variables	Progression Free Survival					Overall Survival				
	N	Univariable Cox model		Multivariable Cox model[1]		N	Univariable Cox model		Multivariable Cox model[1]	
		HR [95%CI]	p-value	HR [95%CI]	p-value		HR [95%CI]	p-value	HR [95%CI]	p-value
Sex										
Female	544	Ref		Ref		632	Ref		Ref	
Male	725	1·19 [0·94, 1·49]	0·14	1·08 [0·86, 1·37]	0·50	804	1·30 [0·99, 1·71]	0·057	1·22 [0·92, 1·62]	0·16
Age at diagnosis, years										
<5	526	Ref		Ref		611	Ref		Ref	
5 to <15	556	1·07 [0·84, 1·36]	0·60	1·20 [0·87, 1·66]	0·26	622	1·01 [0·76, 1·34]	0·93	1·07 [0·73, 1·55]	0·74
≥15	187	1·24 [0·89, 1·75]	0·21	1·36 [0·87, 2·11]	0·18	203	1·07 [0·7, 1·63]	0·76	0·99 [0·58, 1·7]	0·97
Ethnicity										
Non-Hispanic	742	Ref		Ref		894	Ref		Ref	
Hispanic	366	1·27 [0·99, 1·62]	0·061	0·89 [0·63, 1·26]	0·52	372	1·3 [0·97, 1·73]	0·078	0·79 [0·53, 1·19]	0·26
Unknown	161	0·5 [0·32, 0·79]	0·0026	0·75 [0·41, 1·37]	0·36	170	0·26 [0·13, 0·52]	0·00018	0·33 [0·13, 0·8]	0·014
Race										
White	715	Ref		Ref		834	Ref		Ref	
Black	29	1·6 [0·85, 3·03]	0·15	1·41 [0·71, 2·78]	0·33	35	1·88 [0·95, 3·68]	0·068	1·91 [0·9, 4·02]	0·090
Asian	111	0·99 [0·66, 1·49]	0·98	1·15 [0·74, 1·78]	0·55	126	0·62 [0·35, 1·1]	0·11	1·01 [0·55, 1·84]	0·99
Other/unknown	414	0·87 [0·67, 1·12]	0·28	1·43 [0·99, 2·07]	0·059	441	0·9 [0·67, 1·21]	0·48	2·92 [1·88, 4·55]	<0·0001
Diagnosis										
CNS	384	Ref				442	Ref			
Non-CNS	885	0·65 [0·52, 0·81]	<0·0001			994	0·59 [0·46, 0·78]	0·00013		
Underlying malignancy[2]										
CNS	384	Ref				442	Ref			
Germ cell tumor	193	0·29 [0·17, 0·48]	<0·0001			205	0·05 [0·01, 0·19]	<0·0001		
Hepatic tumor (HB or HCC)	158	0·39 [0·25, 0·62]	<0·0001			170	0·27 [0·15, 0·51]	<0·0001		
Neuroblastoma	197	0·93 [0·68, 1·26]	0·63			246	1·01 [0·72, 1·41]	0·95		
Osteosarcoma	260	0·81 [0·6, 1·09]	0·17			293	0·84 [0·6, 1·19]	0·33		
Other	77	0·83 [0·51, 1·34]	0·44			80	0·63 [0·34, 1·18]	0·15		
Stem cell transplant[3]										
No	1004	Ref		Ref		1015	Ref		Ref	
Yes	256	2·16 [1·7, 2·74]	<0·0001	1·27 [0·85, 1·89]	0·25	258	1·86 [1·4, 2·48]	<0·0001	0·68 [0·44, 1·05]	0·084
Unknown	9					163	0·87 [0·4, 1·87]	0·72	2·39 [0·99, 5·73]	0·051
Carboplatin exposure[3]										
No	615	Ref		Ref		621	Ref		Ref	
Yes	200	2·33 [1·71, 3·18]	<0·0001	1·96 [1·31, 2·93]	0·00099	209	1·89 [1·32, 2·71]	0·0005	1·42 [0·89, 2·26]	0·15
Unknown	454	2·63 [2·03, 3·42]	<0·0001	1·4 [0·97, 2·01]	0·069	606	1·96 [1·45, 2·66]	<0·0001	0·66 [0·43, 1·02]	0·062
Vincristine exposure[3]										
No	563	Ref		Ref		661	Ref		Ref	
Yes	685	1·72 [1·34, 2·19]	<0·0001	1·43 [0·81, 2·52]	0·22	754	1·98 [1·48, 2·66]	<0·0001	1·07 [0·55, 2·1]	0·84
Unknown	21	6·19 [3·53, 10·86]	<0·0001	3·96 [1·84, 8·52]	0·00043	21	5·06 [2·43, 10·57]	<0·0001	2·52 [0·97, 6·56]	0·059
CRT dose, Gy[3]										
0	938	Ref		Ref		1067	Ref		Ref	
>0 to ≤ 50	53	1·32 [0·79, 2·19]	0·29	1·61 [0·83, 3·1]	0·16	55	1·25 [0·68, 2·30]	0·48	1·21 [0·55, 2·62]	0·64

>50	278	1·32 [1·03, 1·71]	0·029	1·13 [0·71, 1·79]	0·62	314	1·37 [1·02, 1·84]	0·036	0·77 [0·45, 1·32]	0·35
VP Shunt										
No	643	Ref		Ref		646	Ref		Ref	
Yes	117	1·56 [1·15, 2·11]	0·0044	1·42 [0·97, 2·09]	0·071	117	1·52 [1·07, 2·14]	0·018	1·26 [0·83, 1·94]	0·28
Unknown	509	0·33 [0·25, 0·44]	<0·0001	0·39 [0·27, 0·58]	<0·0001	673	0·19 [0·13, 0·28]	<0·0001	0·15 [0·09, 0·25]	<0·0001
Cisplatin dosing parameters										
Cisplatin total cumulative dose, +100 mg/m^2	1269	0·88 [0·81, 0·96]	0·0043	0·92 [0·83, 1·02]	0·11	1436	0·85 [0·77, 0·94]	0·0020	0·85 [0·75, 0·97]	0·018
Cisplatin prescribed cycle dose, +50 mg/m^2/cycle	1269	1·32 [1·16, 1·5]	<0·0001	1·78 [1·15, 2·75]	0·0091	1436	1·40 [1·21, 1·62]	<0·0001	2·25 [1·35, 3·73]	0·0017
Cisplatin prescribed daily dose, +10 mg/m^2/day	1269	1·02 [0·98, 1·06]	0·32	0·94 [0·88, 1·01]	0·11	1436	1·05 [0·99, 1·10]	0·051	0·99 [0·91, 1·07]	0·75
Cisplatin dose rate, +1 mg/m^2/hour	1269	1·01 [0·99, 1·01]	0·11	0·99 [0·97, 1·01]	0·13	1436	1·01 [0·99, 1·02]	0·072	0·98 [0·96, 0·99]	0·041

[1]Cisplatin dosing parameters were evaluated in a series of nested cox regression models including progressively more granular dosing (Model 2: +cumulative dose; Model 3: +cumulative dose, cycle dose; Model 4: +cumulative dose, cycle dose, daily dose; Model 5: +cumulative dose, cycle dose, daily dose, dose rate); Likelihood Ratio Tests compared each model for progression-free survival (Base Model vs. Model 2, p= 0·19; Models 2 vs. 3, p= 0·022; Models 3 vs. 4, p= 0·034; Models 4 vs. 5, p= 0·11) and overall survival (Base Model vs. Model 2, p= 0·026; Models 2 vs. 3, p= 0·0083; Models 3 vs. 4, p= 0·39; Models 4 vs. 5, p= 0·039). [2]Underlying malignancy was modeled as a strata factor in multivariable cox models. [3]Treatment variables included to additionally account for regimen differences potentially affecting survival within diagnosis strata. CNS = central nervous system tumor; HB or HCC = hepatoblastoma or hepatocellular carcinoma; CRT = cranial radiotherapy; VP shunt – ventriculoperitoneal (or other ventricular) shunt.

Table S7: Multivariable models for moderate/severe hearing loss at end of therapy and progression-free and overall survival

Variables	Progression-free survival					Overall survival				
	N	Univariable Cox model		Multivariable Cox model[1]		N	Univariable Cox model		Multivariable Cox model[1]	
		HR [95%CI]	p-value	HR [95%CI]	p-value		HR [95%CI]	p-value	HR [95%CI]	p-value
Sex										
Female	483	Ref		Ref		547	Ref		Ref	
Male	665	1·24 [0·98, 1·57]	0·079	1·12 [0·88, 1·44]	0·36	727	1·32 [0·99, 1·74]	0·055	1·20 [0·90, 1·61]	0·22
Age at diagnosis, years										
<5	484	Ref		Ref		539	Ref		Ref	
5 to <15	490	1·07 [0·83, 1·37]	0·61	1·17 [0·84, 1·63]	0·36	549	1·03 [0·77, 1·37]	0·85	1·03 [0·70, 1·52]	0·89
≥15	174	1·21 [0·85, 1·72]	0·29	1·18 [0·74, 1·88]	0·49	186	1·08 [0·70, 1·66]	0·74	0·84 [0·48, 1·48]	0·55
Ethnicity										
Non-Hispanic	665	Ref		Ref		781	Ref		Ref	
Hispanic	324	1·24 [0·96, 1·61]	0·096	0·83 [0·58, 1·20]	0·33	327	1·32 [0·98, 1·77]	0·068	0·78 [0·51, 1·19]	0·25
Unknown	159	0·43 [0·27, 0·68]	0·00041	0·65 [0·35, 1·22]	0·18	166	0·18 [0·08, 0·40]	<0·0001	0·27 [0·10, 0·73]	0·0096
Race										
White	633	Ref		Ref		720	Ref		Ref	
Black	25	1·65 [0·84, 3·22]	0·14	1·24 [0·60, 2·57]	0·56	28	1·93 [0·94, 3·94]	0·072	1·66 [0·75, 3·69]	0·22
Asian	102	0·99 [0·65, 1·49]	0·95	1·10 [0·70, 1·75]	0·67	115	0·62 [0·35, 1·10]	0·10	1·03 [0·56, 1·91]	0·92
Other/unknown	388	0·82 [0·63, 1·07]	0·14	1·51 [1·02, 2·23]	0·039	411	0·80 [0·59, 1·10]	0·17	2·93 [1·84, 4·65]	<0·0001
Diagnosis										
CNS	334	Ref				378	Ref			
Non-CNS	814	0·61 [0·48, 0·78]	<0·0001			896	0·59 [0·45, 0·77]	0·00014		
Underlying malignancy[2]										
CNS	334	Ref				378	Ref			
Germ cell tumor	178	0·29 [0·18, 0·49]	<0·0001			185	0·05 [0·01, 0·19]	<0·0001		
Hepatic tumor (HB or HCC)	142	0·33 [0·20, 0·54]	<0·0001			150	0·26 [0·14, 0·51]	<0·0001		
Neuroblastoma	191	0·87 [0·63, 1·19]	0·38			227	0·96 [0·68, 1·35]	0·79		
Osteosarcoma	240	0·75 [0·55, 1·03]	0·073			270	0·85 [0·60, 1·21]	0·37		
Other	63	0·84 [0·51, 1·40]	0·51			64	0·58 [0·29, 1·15]	0·12		
Stem cell transplant[3]										
No	894	Ref		Ref		901	Ref		Ref	
Yes	245	2·05 [1·61, 2·62]	<0·0001	1·01 [0·67, 1·51]	0·98	246	1·70 [1·27, 2·28]	0·00040	0·50 [0·32, 0·78]	0·0021
Unknown	9					127	0·54 [0·20, 1·46]	0·22	1·26 [0·42, 3·74]	0·68
Carboplatin exposure[3]										
No	575	Ref		Ref		580	Ref		Ref	
Yes	189	2·39 [1·74, 3·27]	<0·0001	2·26 [1·50, 3·41]	0·00011	194	2·01 [1·40, 2·89]	0·00016	1·83 [1·13, 2·96]	0·013
Unknown	384	2·89 [2·21, 3·79]	<0·0001	1·57 [1·07, 2·30]	0·021	500	2·19 [1·60, 3·00]	<0·0001	0·77 [0·48, 1·21]	0·25
Vincristine exposure[3]										
No	515	Ref		Ref		589	Ref		Ref	
Yes	614	1·75 [1·36, 2·25]	<0·0001	1·41 [0·76, 2·59]	0·28	666	2·03 [1·50, 2·75]	<0·0001	1·15 [0·52, 2·52]	0·73
Unknown	19	7·47 [4·24, 13·15]	<0·0001	4·18 [1·89, 9·27]	0·00042	19	6·02 [2·87, 12·6]	<0·0001	3·21 [1·14, 9·00]	0·027
CRT dose, Gy[3]										
0	866	Ref		Ref		961	Ref		Ref	
>0 to ≤ 50	51	1·23 [0·73, 2·09]	0·43	1·46 [0·73, 2·94]	0·28	53	1·11 [0·58, 2·11]	0·75	1·24 [0·54, 2·85]	0·61

>50	231	1·43 [1·10, 1·86]	0·0074	1·15 [0·71, 1·87]	0·57	260	1·48 [1·09, 2·00]	0·011	0·96 [0·54, 1·71]	0·88
VP shunt										
No	565	Ref		Ref		567	Ref		Ref	
Yes	102	1·65 [1·21, 2·25]	0·0017	1·50 [0·99, 2·25]	0·052	102	1·53 [1·08, 2·17]	0·017	1·37 [0·87, 2·15]	0·17
Unknown	481	0·30 [0·23, 0·41]	<0·0001	0·38 [0·26, 0·57]	<0·0001	605	0·14 [0·09, 0·22]	<0·0001	0·14 [0·08, 0·24]	<0·0001
Cisplatin dosing parameters										
Cisplatin total cumulative dose, +100 mg/m^2	1,148	0·88 [0·81, 0·97]	0·0063	0·93 [0·84, 1·04]	0·20	1,274	0·88 [0·79, 0·97]	0·015	0·89 [0·78, 1·02]	0·11
Cisplatin prescribed cycle dose, +50 mg/m^2/cycle	1,148	1·29 [1·13, 1·48]	0·00012	1·85 [1·19, 2·89]	0·0065	1,274	1·38 [1·19, 1·61]	<0·001	2·60 [1·49, 4·56]	0·00082
Cisplatin prescribed daily dose, +10 mg/m^2/day	1,148	1·02 [0·98, 1·06]	0·44	0·95 [0·88, 1·02]	0·13	1,274	1·05 [1·00, 1·10]	0·052	1·00 [0·92, 1·09]	0·96
Cisplatin dose rate, +1 mg/m^2/hour	1,148	1·01 [0·99, 1·01]	0·18	0·98 [0·97, 1·01]	0·10	1,274	1·01 [0·99, 1·02]	0·13	0·98 [0·96, 0·99]	0·033
Hearing loss at end of therapy										
No	701	Ref		Ref		779	Ref		Ref	
Yes	447	1·00 [0·79, 1·26]	0·99	0·93 [0·71, 1·22]	0·60	495	1·01 [0·77, 1·33]	0·96	0·85 [0·62, 1·16]	0·30

[1]Cisplatin dosing parameters were evaluated in a series of nested cox regression models including progressively more granular dosing (Model 2: +cumulative dose; Model 3: +cumulative dose, cycle dose; Model 4: +cumulative dose, cycle dose, daily dose; Model 5: +cumulative dose, cycle dose, daily dose, dose rate; Model 6: cumulative dose, cycle dose, daily dose, dose rate, hearing loss at end of therapy); Likelihood Ratio Tests compared each model for progression-free survival (Base Model vs. Model 2, p= 0·27; Models 2 vs. 3, p= 0·020; Models 3 vs. 4, p= 0·035; Models 4 vs. 5, p= 0·091; Models 5 vs. 6, p= 0·60) and overall survival (Base Model vs. Model 2, p= 0·11; Models 2 vs. 3, p= 0·0045; Models 3 vs. 4, p= 0·51; Models 4 vs. 5, p= 0·031; Models 5 vs. 6, p= 0·30). [2]Underlying malignancy was modeled as a strata factor in multivariable cox models. [3]Treatment variables included to additionally account for regimen differences potentially affecting survival within diagnosis strata. CNS = central nervous system tumor; HB or HCC = hepatoblastoma or hepatocellular carcinoma; CRT = cranial radiotherapy; VP shunt – ventriculoperitoneal (or other ventricular) shunt.