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ORIGINAL ARTICLE

Impact of radiation technique, radiation fraction dose, and total cisplatin dose on hearing

Retrospective analysis of 29 medulloblastoma patients

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Abstract
Purpose To analyze the incidence and degree of sensorineural hearing loss (SNHL) resulting from different radiation techniques, fractionation dose, mean cochlear radiation dose (D_{mean}), and total cisplatin dose.
Material and methods In all, 29 children with medulloblastoma (58 ears) with subclinical pretreatment hearing thresholds participated. Radiotherapy (RT) and cisplatin had been applied sequentially according to the HIT MED Guidance. Audiological outcomes up to the latest follow-up (median 2.6 years) were compared.
Results Bilateral high-frequency SNHL was observed in 26 patients (90%). No significant differences were found in mean hearing threshold between left and right ears at any frequency. A significantly better audiological outcome ($p < 0.05$) was found after tomotherapy at the 6 kHz bone-conduction threshold (BCT) and left-sided 8 kHz air-conduction threshold (ACT) than after a combined radiotherapy technique (CT). Fraction dose was not found to have any impact on the incidence, degree, and time-to-onset of SNHL. Patients treated with CT had a greater risk of SNHL at high frequencies than tomotherapy patients even though D_{mean} was similar. Increase in severity of SNHL was seen when the total cisplatin dose reached above 210 mg/m², with the highest abnormal level found 8–12 months after RT regardless of radiation technique or fraction dose.
Conclusion The cochlear radiation dose should be kept as low as possible in patients who receive simultaneous cisplatin-based chemotherapy. The risk of clinically relevant HL was shown when D_{mean} exceeds 45 Gy independent of radiation technique or radiation regime. Cisplatin ototoxicity was shown to have a dose-dependent effect on bilateral SNHL, which was more pronounced in higher frequencies.

Keywords Hearing loss, sensorineural · Radiotherapy, intensity-modulated · Fraction dose · Cochlea · Bone conduction

Effekte von Bestrahlungstechnik, Fraktionierung und Cisplatin-Gesamtdosis auf das Hörvermögen

Retrospektive Analyse von 29 Patienten mit Medulloblastom

Zusammenfassung
Ziel Analyse von Inzidenz und Schweregrad einer sensorineuralen Schwerhörigkeit („sensorineural hearing loss“, SNHL) infolge der Wirkung unterschiedlicher Bestrahlungstechniken, Fraktionierungen, mittlerer kochleärer Strahlendosen (D_{mean}) und Cisplatin-Gesamtdosen.
Material und Methoden Es wurden 29 Kinder (entsprechend 58 Ohren) mit Medulloblastom und mit subklinischen prätherapeutischen Hörschwellen analysiert. Radiotherapie und Cisplatin-basierte Chemotherapie wurden sequenziell gemäß dem HIT-MED-Protokoll eingesetzt. Verglichen wurden unter laufender Therapie und posttherapeutisch gewonnene audiologische Ergebnisse (mediane Nachbeobachtungszeit 2,6 Jahre).

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Ergebnisse Eine bilaterale Hochtonschwerhörigkeit wurde bei 26 (90 %) Patienten beobachtet. Ein Vergleich linker und rechter Ohren zeigte bei keiner Frequenz einen signifikanten Unterschied im mittleren Hörverlust. Eine signifikant geringere Schädigung ($p < 0{,}05$) ergab sich für Tomotherapie bei 6 kHz in der Knochenleitungs- und linksseitig bei 8 kHz in der Luftleitungsmessung im Vergleich zu kombinierter Bestrahlungstechnik. Die Fraktionierungsdosis zeigte keinen Effekt auf Inzidenz, Schweregrad und Latenzzeit der Schwerhörigkeit. Bei gleicher D_{mean} ergab sich nach kombinierter Bestrahlungstechnik ein höheres Risiko für einen Hörverlust im Hochtonbereich als nach einer Tomotherapie. Eine Zunahme des Schweregrads der Hörschädigung wurde bei einer Cisplatin-Gesamtdosis über 210 mg/m² festgestellt, mit den höchsten abnormen Werten 8–12 Monate nach Ende der Bestrahlung, unabhängig von der Bestrahlungstechnik und von Fraktionierungsschemata. *Schlussfolgerung* Die Innenohrdosis/Dosis an der Kochlea sollte für Patienten mit simultaner Cisplatin-Gabe so niedrig wie möglich gehalten werden. Unabhängig von Fraktionierung und Technik besteht das Risiko eines klinisch relevanten Hörverlustes bei einer mittleren Innenohrdosis >45 Gy. Zudem zeigte die Ototoxizität durch Cisplatin einen dosisabhängigen Effekt auf einen bilateralen, besonders in den hohen Frequenzen betonten SNHL.

Schlüsselwörter Sensorineuraler Hörverlust · Intensitätsmodulierte Strahlentherapie · Fraktionierte Dosis · Kochlea · Knochenleitung

Current multimodal treatment of medulloblastoma includes surgery of the primary tumor, adjuvant craniospinal irradiation (CSI) with add-on dose escalation to the posterior cranial fossa (PCF), and, if required, an additional boost to the macroscopic residual tumor and neuronal metastases, and cisplatin-based chemotherapy. Five-year overall survival rates are 80% and 70%, respectively, in patients with standard-risk and high-risk medulloblastoma treated using the current combined treatment concept [1–7].

One possible side-effect of the above treatment is sensorineural hearing loss (SNHL) resulting from the synergistic ototoxic effect of cranial radiotherapy (RT) and cisplatin-based treatment [1, 8–11]. In the limited number of studies in the literature, a larger cochlear irradiation dose was shown to correlate with incidence, severity, time-to-onset, and reversibility of SNHL, with a more severe effect found in the high-frequency range of hearing [12–14]. Cisplatin is a known ototoxic drug causing early onset, bilateral high-frequency hearing loss (HL) [1, 8–10, 12, 15, 16]. Cochlear radiation dose (D_{mean}) does not have a precisely defined upper limit in cases of simultaneous cranial RT and cisplatin treatment. The upper limit may differ from the limit of 45 Gy, which is accepted for cases of cranial RT without cisplatin [17–19]. An ototoxic threshold dose for cisplatin has also not been clearly determined. Several modern radiation techniques that limit the radiation dose given to the cochlea have been developed. These include intensity-modulated radiation therapy (IMRT), including stereotactic technique [20–24], and proton therapy [25, 26]. IMRT techniques are capable of achieving a more conformal dose distribution than three-dimensional RT, thus, reducing the radiation dose to the cochlea. Finally, some retrospective analyses found no significant effect of radiation fraction dose via cranial RT on the incidence and degree of SNHL [12, 27].

The present study shows retrospective analyses of the development of SNHL in medulloblastoma patients with respect to different radiation techniques, fractionation dose, cochlear D_{mean}, and total cisplatin dose. The incidence and degree of SNHL was evaluated by determining the bone- and air-conduction threshold values (BCT/ACT) within a frequency range including those frequencies most responsible for the perception of human speech (500 Hz–8 kHz). The audiological data of 29 medulloblastoma patients treated in our department according to current treatment guidance were analyzed (Fig. 1, Supplemental Data).

Methods and materials

A total of 38 medulloblastoma patients were eligible for the treatment between 2000 and 2014. These patients had primary diagnosed, localized (standard risk) or metastatic (high risk) medulloblastoma. Of them, 29 patients who had clinically insignificant pretreatment hearing thresholds and at least 12 months postradiation audiograms were included in the retrospective analyses of incidence, severity, and time course of hearing impairment. Patient demographics are presented in Table 1. Each ear of the 29 patients was treated as an individual subject, so audiological data of 58 ears were analyzed. The effects of radiation technique and fraction dose, as well as cochlear D_{mean} and total cisplatin dose on the development of SNHL were evaluated. Symmetry of HL between each patient's ears (side difference) was also considered.

Postoperative RT was applied according to one of two different radiotherapy regimes (conventionally fractionated [CRT, $N = 17$] or hyperfractionated [HRT, $N = 12$]), using of one of two treatment techniques: tomotherapy in supine position ($N = 12$) or combined technique (CT) using dorsoventral static field for CSI and an IMRT (Sliding Window technique) boost on the PCF and the residual tumor (where required) in the abdominal position ($N = 17$).

The effect of radiation technique on the development of HL was assessed by comparing the results of the tomotherapy and CT groups in each fractionation regime. The impact

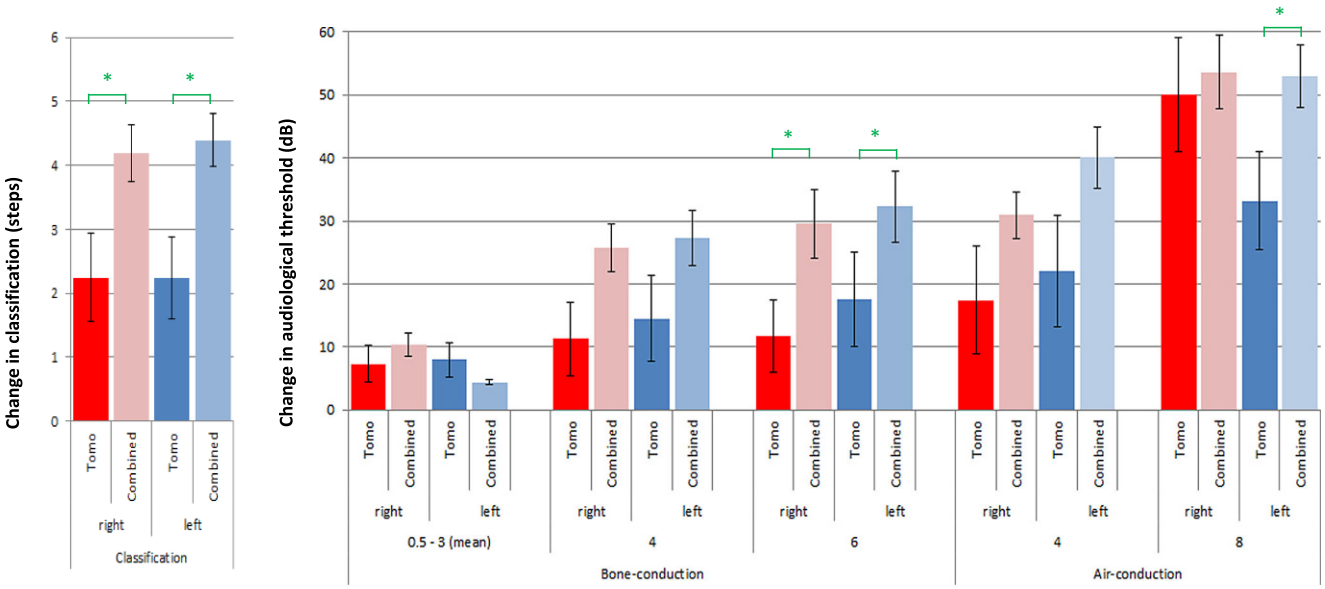

Fig. 1 Changes in the hearing threshold over postradiation time. Audiological classification, radiotherapeutic technique (tomotherapy/combined), ear (right/left), frequency (kHz), and transducer (bone-/air-conduction)

of fraction dose was evaluated by comparing the results of the CRT and HRT fractionation groups for each radiation technique. The relationship between SNHL and cochlear D_{mean} was evaluated in D_{mean} range from 35 to 65 Gy in 5 Gy intervals using the audiological results of the latest follow-up.

Results of all audiological tests that had taken place, including BCT and ACTs, were analyzed and compared between the following time points: (1) prior to radiation up to the 3rd cisplatin cycle (T1) vs. most recent follow-up audiometry (T2) to assess the impact of radiation technique/fraction dose on the incidence and degree of SNHL; (2) during cisplatin therapy—prior to radiation treatment up to the 3rd cycle (Ta) vs. 3rd to 5th cycle (Tb) vs. following the last cisplatin cycle up to 12 months (Tc) to evaluate any changes in hearing threshold according to the various total cisplatin doses. The audiological results prior to radiation and up to the beginning of the 3rd cisplatin cycle were combined into one group for analysis, on the basis of Schell and colleagues' observation that no relevant ototoxicity resulted from cisplatin doses up to 270 mg/m² in patients receiving cranial RT [16].

Audiometry

All patients underwent baseline audiometry before RT and postradiation audiometry took place usually every 2–3 months. Audiological thresholds were measured using age-appropriate, ear-specific behavioral measurement techniques. Pure-tone stimuli at a range of frequencies (0.5–6 kHz for bone-conduction and 0.25–8 kHz for air-conduction) were used (based on a recommendation by Bhandare et al. [17]) as well as the Muenster classification scale (Schmidt et al. [28]), an ordinal scale of severity of ototoxicity [17, 28]. Thresholds for right and left ears were examined separately for each patient. Hearing was considered to be clinically insignificant if classification of the audiogram using the Muenster classification scheme was ≤2a (corresponding to the worst threshold being ≤40 dB HL at 4 kHz or above and thresholds at all other frequencies being ≤20 dB HL) [9, 28]. Patients with initial audiograms outside of this range were excluded from the study.

Radiation therapy

Detailed description of the radiation techniques is presented in the Supplemental Data.

Chemotherapy

Eight cycles of adjuvant chemotherapy, including cisplatin with a total dose of 560 mg/m², were administered for patients with standard-risk disease who were allocated to CRT. Four cycles of chemotherapy with a total cisplatin dose of 280 mg/m² were administered after HRT in patients with high-risk disease. The cisplatin dose was administered at 70 mg/m² per cycle at 6-week intervals. The dose schedules, route and duration of administration, as well as hematologic criteria for chemotherapy are described in detail in the treatment protocol (Fig. 1, Supplemental Data).

Table 1 Clinical variables for patient population

Fractionation				CRT		HRT	
Technique				Tomotherapy	Combined RT	Tomotherapy	Combined RT
No. of patients (male/female)				7(4/3)	10(4/6)	5(3/2)	7(4/3)
Age at the time of RT, years, median/range				11/4.2–17.8	7.5/4.8–10.2	11.5/6.7–16.4	8.7/5.8–11.6
Follow-up, years, median/range				2.8/1.6–5.7	4.1/1.4–9	3.8/1.4–5.7	3.5/1.6–8.7
Metastases	No metastases			3	6	0	0
	Tumor cells in liquor			4	5	0	0
	Macroscopic intracerebral and/or intraspinal			0	0	4	7
Mean/Maximal cochlear dose, Gy ± SD			Right	45 ± 4/51 ± 3	47 ± 4/55 ± 2	54 ± 4/59 ± 2	57 ± 3/65 ± 4
			Left	45 ± 4/52 ± 4	46 ± 2/56 ± 3	55 ± 4/58 ± 3	56 ± 4/64 ± 5
Total cisplatin dose, mg/m^2				560		280	
Audiological results, last follow-up	Bone-conduction mean dB ± SD	Mean 0.5–3 kHz	Right	6 ± 7	8 ± 6	9 ± 7	8 ± 7
			Left	5 ± 4	7 ± 5	9 ± 7	9 ± 7
		4 kHz	Right	12 ± 6	20 ± 15	19 ± 17	21 ± 16
			Left	12 ± 5	20 ± 15	22 ± 15	19 ± 13
		6 kHz	Right	14 ± 8	26 ± 16	25 ± 17	28 ± 18
			Left	12 ± 6	24 ± 15	30 ± 15	27 ± 13
	Air-conduction mean dB ± SD	4kHz	Right	22 ± 17	24 ± 17	27 ± 17	35 ± 19
			Left	18 ± 5	31 ± 14	37 ± 18	33 ± 11
		8 kHz	Right	41 ± 17	39 ± 17	46 ± 20	52 ± 17
			Left	37 ± 13	42 ± 13	48 ± 19	52 ± 15
	Classification, mean/range		Right	2b/2a–3a	2b/1–3c	2c/2a–3c	2c/1–3c
			Left	2b/2a–3a	2c/1–3c	3a/2a–3c	3a/2b–3c

CRT conventionally fractionated radiotherapy, *HRT* hyperfractionated radiotherapy, *RT* radiotherapy, *SD* standard deviation

Statistical analyses

An analysis of covariance (ANCOVA) was performed using the mean values of the audiological dependent variables (4 and 6 kHz BCT for each ear, 4, 6, and 8 kHz ACT for each ear) and positions and treatment techniques as categorical independent variables. The effect of the variable age (covariate) was controlled. The homogeneity of variance assumption was tested with Levene's test of equality of error variances. A univariate logistic regression analysis was performed to assess the degree of SNHL at all frequencies on the latest follow-up audiometric test for patients with cochlear D_{mean} within the 35–65 Gy range. Multiple regression analysis was also used to verify the interaction effects between techniques and groups. Data were analyzed using descriptive statistics, Wald test, analysis of variance, and ordinal regression. The threshold for statistical significance was defined at $p < 0.05$. The statistical analysis was performed using SPSS software (IBM SPSS Statistics 24.0 and 22.0).

Results

Descriptive statistics are shown in Table 1. The mean duration of follow-up varied as follows: 2.8 years (CRT)/3.8 years (HRT) for tomotherapy, 4.1 years (CRT)/3.5 years (HRT) for CT. The average cochlear D_{means} were 45 ± 4 Gy right, 45 ± 4 Gy left (tomotherapy), and 47 ± 4/46 ± 5 Gy (CT) for the CRT group, 54 ± 4/55 ± 4 Gy (tomotherapy) and 57 ± 3/56 ± 4 Gy (CT) for the HRT group. To the contrary, D_{max} values were found significantly lower for the tomotherapy in both fractionations group (Table 1). Smaller cochlear volume was obtained in the tomotherapy radiation plans, where it averaged 0.4 cm^3 (range 0.2–0.7 cm^3) compared to 0.8 cm^3 (range 0.5–1.2 cm^3) in conventional RT and 0.6 cm^3 (range 0.4–1.0 cm^3) in Sliding Window treatment plans.

Bilateral high-frequency hearing impairment was observed in 26 out of 29 patients at T2. No significant differences in mean hearing threshold at any frequency between left and right ears at any of the three time points was found. Age was found to have a small effect (chiefly

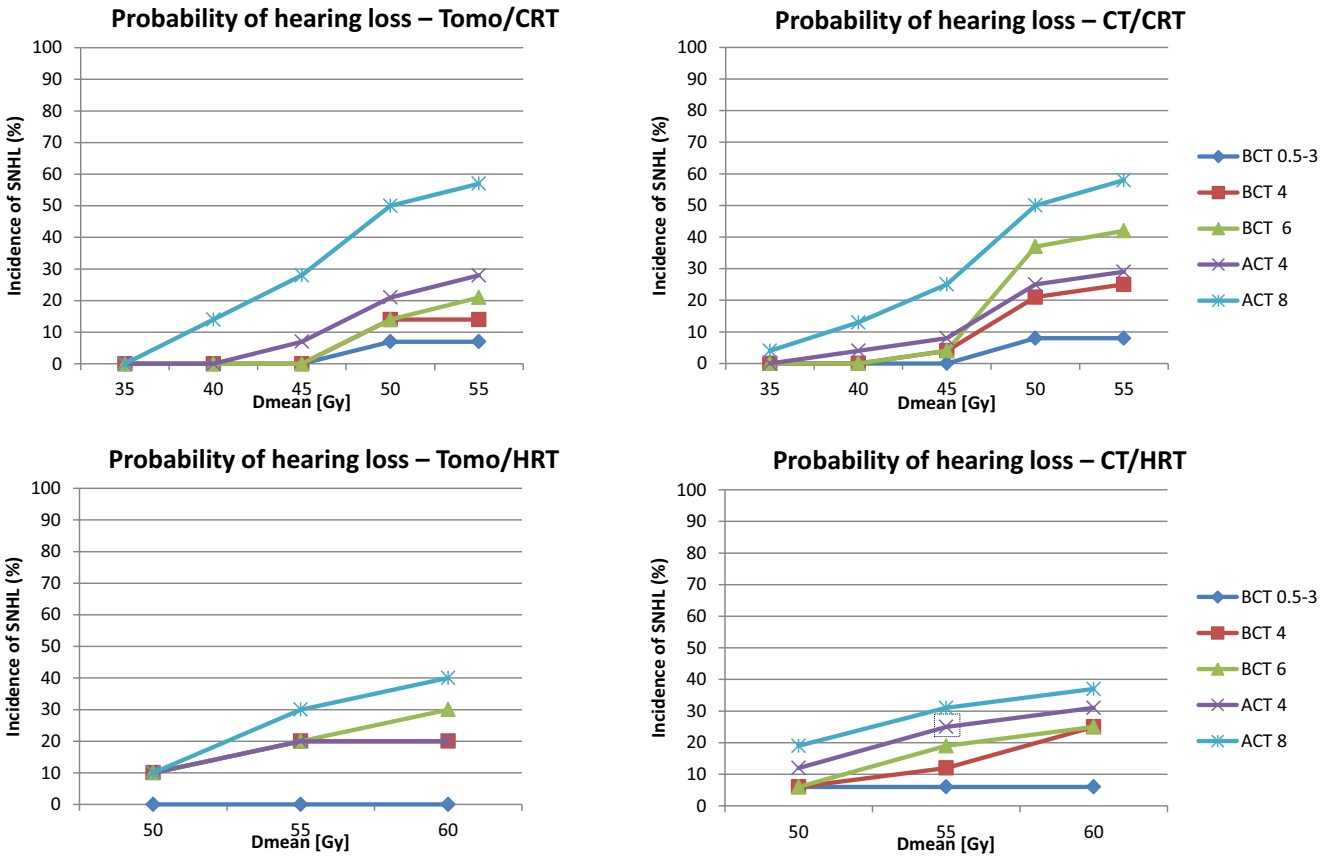

Fig. 2 Mean dose response for hearing loss in low, intermediate, and high frequencies with relation to cochlear D_{mean}, radiation technique and fraction dose. *CT* combined technique; *CRT* once-daily fractionation; *HRT* twice-daily fractionation. Significant difference in hearing loss between radiation techniques is marked with quadrant (CT/HRT group), *BCT* bone-conduction threshold, *ACT* air-conduction threshold

on audiological results on the right side) but was not systematic.

A significant difference between audiological thresholds at T1 and T2 was found irrespective of fractionation group. Crucially, significant differences were found between the two radiation technique groups (tomotherapy vs CT) in the degree of change in hearing thresholds between T1 and T2 according to the Muenster Classification grade (p = 0.03 right ear; p = 0.01 left ear), 6 kHz BCT (p = 0.02 right, p = 0.01 left), and left-sided 8 kHz ACT (p = 0.047) (Fig. 1). Eight patients (13 ears, 44%) in the combined treatment group had audiological classifications ≥3b (reflecting SNHL of moderate–severe degree or worse) in at least one ear, whereas only 2 patients (3 ears, 13%) in the tomotherapy group had similar degrees of HL.

The impact of cochlear D_{mean} on the incidence of SNHL was separately evaluated for radiation techniques and fractionation dose (Fig. 2). The absolute hearing threshold was measured at the latest follow-up (20–108 months after RT). In all, 30% of ears in the CRT group which had received D_{mean} ≤45 Gy demonstrated high-frequency SNHL (8 kHz ACT >40 dB HL) irrespective of the radiation technique. At a mid-high frequency (4 kHz ACT), the incidence of HL was 6% of ears after tomotherapy and 9% after CT (p = 0.15). For patients with a D_{mean} of 46–55 Gy, the hearing threshold for most patients increased to greater than 40 dB HL at mid- and high-frequencies (classification ≥ 2b according to the Muenster classification), which corresponds to a clinically relevant degree of SNHL. The incidence of high-frequency SNHL in the group with a cochlear D_{mean} >55 Gy increased to 53% in the CRT group and 30% in the HRT group with no significant difference found between radiation techniques (Fig. 2). A significant difference between techniques was found for mid-high frequencies in the HRT group (20% tomotherapy vs. 25% CT, p = 0.048). Thus, an enhanced risk of hearing impairment for similar D_{mean} values was greater at high frequencies.

The largest increase in hearing threshold occurred at 8 kHz (ACT) and averaged 46 ± 18 dB (right ear) and 44 ± 15 dB (left ear) for those treated with tomotherapy in the CRT group, and 55 ± 10 dB (right) and 56 ± 14 dB (left) in the HRT group. After CT, the increase in hearing threshold at 8 kHz was 42 ± 17 dB (right) and 45 ± 12 dB (left) in the CRT group, and 57 ± 11 dB (right) and 55 ± 12 dB (left) in the HRT group. The Wald χ^2 test (two-sided) revealed significantly less change in hearing threshold for the left

Table 2 Wald χ^2 test indicating the relationship between hearing loss (last follow-up audiometry) and radiation technique/fraction dose

	Frequence	Univariate analysis (CI)	*p*-Value	Standard error	Beta	T
Right Ear, CRT vs HRT In CT	BCT 4 Hz	–128.55–91.93	0.69	14.98	–0.17	–0.39
	BCT 6 Hz	–156.77–109.44	0.76	17.20	–0.13	–0.29
	ACT 4 Hz	–154.86–80.47	0.84	16.13	–0.08	–0.20
	ACT 8 Hz	–151.90–61.12	0.65	14.47	–0.17	–0.45
Right Ear, CRT vs HRT in Tomo	BCT 4 Hz	–90.14–277.20	0.15	18.00	0.83	1.66
	BCT 6 Hz	–180.68–164.59	0.51	16.92	0.37	0.67
	ACT 4 Hz	–205.66–329.81	0.67	26.24	0.26	0.44
	ACT 8 Hz	–165.10–304.33	0.77	23.00	0.18	0.23
Right Ear, Tomo vs CT In CRT	BCT 4 Hz	–124.32–88.27	0.19	9.35	–0.36	–1.38
	BCT 6 Hz	–151.28–96.39	0.27	10.39	–0.32	–1.16
	ACT 4 Hz	–154.98–97.49	0.95	11.10	–0.02	–0.06
	ACT 8 Hz	–142.25–99.17	0.63	10.62	0.13	0.48
Right Ear, Tomo vs CT In HRT	BCT 4 Hz	–114.51–336.71	0.62	13.39	–0.18	–0.50
	BCT 6 Hz	–224.77–241.82	0.87	13.85	–0.62	–0.16
	ACT 4 Hz	–229.45–328.12	0.61	16.55	–0.21	–0.53
	ACT 8 Hz	–218.88–257.11	0.75	14.12	–0.12	–0.33
Left Ear, CRT vs HRT In CT	BCT 4 Hz	–87.33–82.13	0.60	12.09	–0.20	–0.53
	BCT 6 Hz	–95.10–87.24	0.77	12.57	–0.11	–0.28
	ACT 4 Hz	–76.68–75.75	0.97	10.88	0.12	0.34
	ACT 8 Hz	–73.62–72.87	0.67	10.45	–0.16	–0.43
Left Ear, CRT vs HRT In Tomo	BCT 4 Hz	–91.99–237.48	0.08	18.74	0.95	2.05
	BCT 6 Hz	–186.84–187.91	0.17	21.31	0.68	1.52
	ACT 4 Hz	–192.34–209.56	0.85	22.86	0.11	0.18
	ACT 8 Hz	–151.27–271.28	0.20	24.03	0.73	1.42
Left Ear, Tomo vs CT In CRT	BCT 4 Hz	–101.30–64.91	0.18	8.73	–0.35	–1.39
	BCT 6 Hz	–111.17–63.47	***0.04***	8.60	–0.47	–1.94
	ACT 4 Hz	–88.98–62.70	0.69	7.97	–0.10	–0.40
	ACT 8 Hz	–85.92–62.60	0.10	7.80	–0.43	–1.77
Left Ear, Tomo vs CT In HRT	BCT 4 Hz	–64.78–284.50	0.38	11.32	0.28	0.98
	BCT 6 Hz	–157.08–260.41	0.40	13.69	0.32	0.89
	ACT 4 Hz	–162.20–240.23	0.80	13.06	–0.91	–0.25
	ACT 8 Hz	–112.31–295.49	0.65	13.27	0.15	0.46

CT combined technique; *CRT* once-daily fractionation; *HRT* twice-daily fractionation, *CI* confidence interval

ear at 6 kHz BCT ($p = 0.046$) in patients treated with CRT/tomotherapy (Table 2). Fig. 3 presents dot plots reflecting the relationship between cochlear D_{mean} and severity of HL on the left side at mid-high and high frequencies obtained from 28 ears (14 patients) treated with once-daily fractionation.

The HL which occurred at mid-high and high frequencies was bilateral across the course of cisplatin treatment and follow-up, and no significant side difference for right vs left ears was observed. Total cisplatin dose correlated linearly with increases in HL: >140 mg/m^2—no clinically relevant HL; 210–350 mg/m^2—mild HL (20–40 dB HL at ≥4 kHz); 350–560 mg/m^2—worse HL (41–60 dB HL at ≥4 kHz). No significant difference between radiation techniques was found on this analysis of increasing total cisplatin dose and increasing HL (Fig. 4). Two further findings are also of interest: (1) hearing threshold levels continued to increase up to 8–12 months after RT in both fractionation groups despite the fact that patients in the HRT group received a lower total cisplatin dose (560 mg/m^2 vs 280 mg/m^2); (2) increase in hearing thresholds at mid and high frequencies was more pronounced in the CT subgroup of the CRT group and the tomotherapy subgroup of the HRT group (Fig. 4).

No additive ototoxicity resulting from the carboplatin applied before RT in the HRT group was observed.

Discussion

The number of studies evaluating the synergistic ototoxic effect of cranial RT and sequential platinum-based

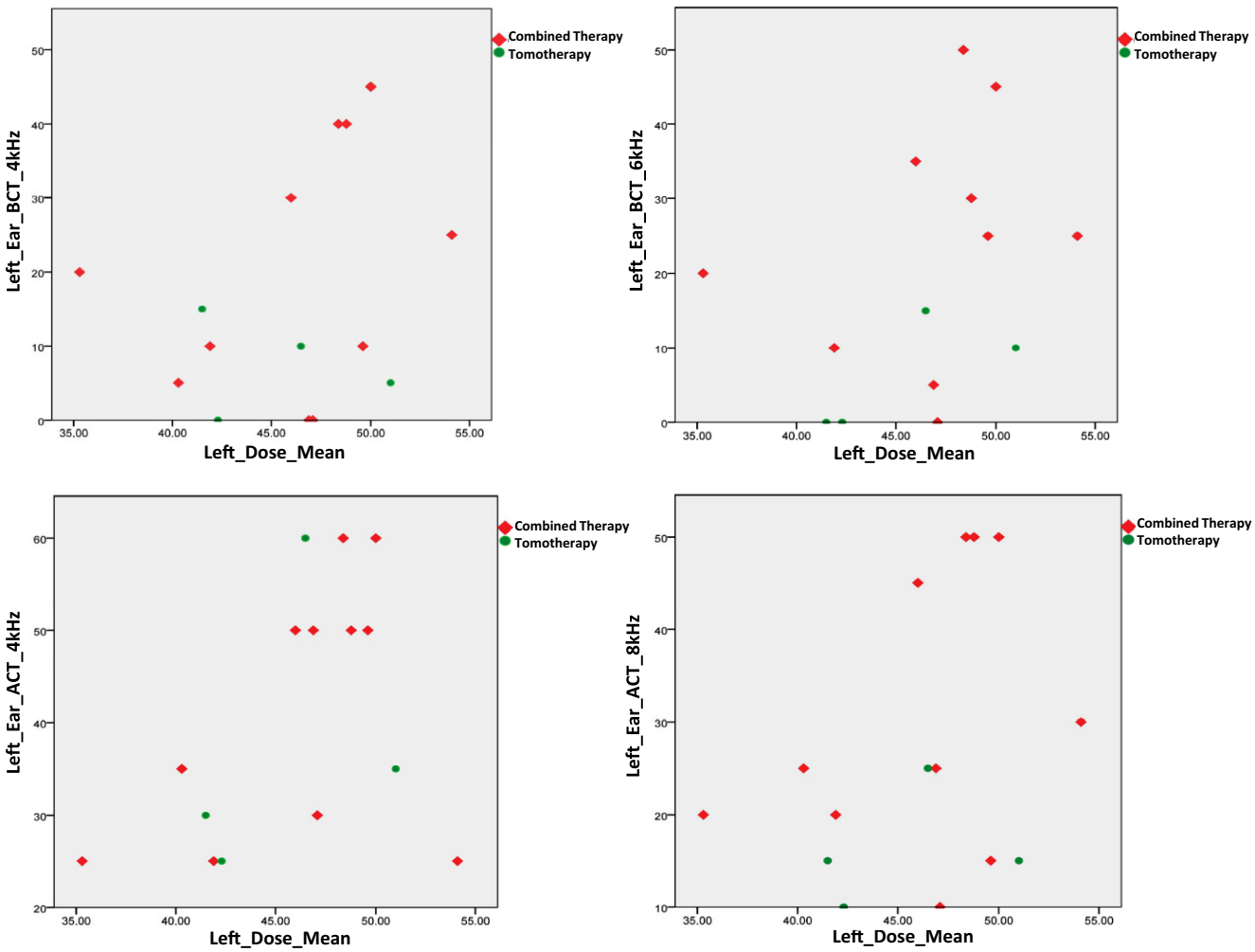

Fig. 3 Dot plot of hearing thresholds in mid-high and high frequencies in the left ear at latest follow-up with conventionally fractionated tomotherapy vs. combined technique. *SNHL* sensorineural hearing loss, *Tomo/CRT* tomotherapy/once-daily fractionation, *CT/CRT* combined technique/once-daily fractionation, *Tomo/HRT* tomotherapy/twice-daily fractionation, *CT/HRT* combined technique/twice-daily fractionation, *BCT* bone-conduction threshold, *ACT* air-conduction threshold

chemotherapy in medulloblastoma patients is very limited [1–3, 10, 11, 21, 29]. Despite the retrospective design, this is the first study that comparatively analyses the relationship between hearing impairment and radiation technique in medulloblastoma patients.

Key findings to emerge from this study are the following: (1) Patients whose radiotherapy treatment was tomotherapy alone demonstrated less deterioration in hearing thresholds in mid-high frequencies (6 kHz BCT, 8 kHz ACT) in both ears over the long-term than those treated with CT despite not relevant difference in cochlear D_{mean} between techniques (Fig. 1). (2) A linear correlation between cochlear D_{mean} and change in hearing thresholds was found, revealing clinically relevant HL (>40 dB HL at ≥4 kHz) for D_{mean} exceeding 45 Gy independent of radiation technique or fractionation regime. (3) Fraction dose did not result in a significant difference in the severity of HL but may have contributed to the incidence of SNHL (Fig. 2). (4) Hearing thresholds appeared to stay stable up to a total cisplatin dose of 210 mg/m^2, at which point mid-high and high frequency hearing thresholds worsened. The degree of change was lower in the tomotherapy/HRT group through to the latest follow-up.

Appropriate interpretation of the significantly greater hearing loss found at 6 kHz BCT in the CRT/tomotherapy group is unclear. BCTs at frequencies above 4 kHz have questionable reliability in individual patients because much of the signal becomes inadvertently air-conducted, leading to unpredictable levels being delivered to the patient [30]. Whether the effect could be expected to be similarly variable across individuals and therefore accounted for within the finding of a significant group-level difference is debatable.

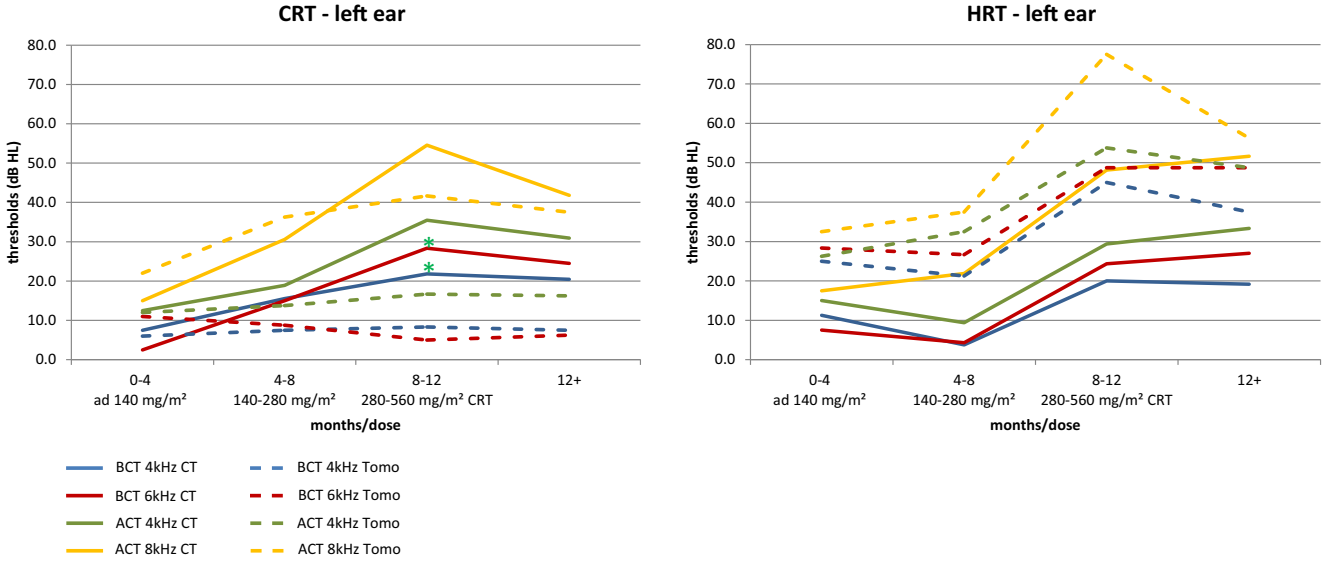

Fig. 4 Hearing changes in the absolute threshold of the left ear at different total cisplatin doses. A comparative analysis of hearing loss in mid-high and high frequencies in patients treated with tomotherapy or combined techniques (*CT*), provided in once-daily (*CRT*) or twice-daily fractionation (*HRT*). *Asterisk* indicates significant difference in hearing loss between radiation techniques. *BCT* bone-conduction threshold, *ACT* air-conduction threshold

Many researchers consider D_{mean} to represent the dosimetric index of the cochlea for cranial irradiation because of the cochlea's small size and potential inclusion in the dose gradient [13, 17, 20]. Interestingly, tomotherapy patients demonstrated superior hearing outcomes in the mid-high frequencies compared to patients treated with CT even though the difference in cochlear D_{mean} was not relevant. In our opinion, there are several possible reasons explaining this result: (1) lower D_{max} for the cochlea and steeper dose gradient with tomotherapy; (2) better imaging modalities for treatment planning, and as a result—smaller cochlear volume in tomotherapy radiation plans; (3) radiation position; and (4) probable decrease in biologic effect. Analysis of the variations in treatment setup assumes that the cochlea received the full radiation dose with 2-dimensional (2D) conventional RT (Supplemental Data). On the contrary, an average of 69% of the prescribed dose was received by the cochlea through tomotherapy. This finding agrees with data found by Huang et al. [20], who determined that 68% of the prescribed dose was delivered in medulloblastoma patients treated with IMRT. Tomotherapy delivered a lower D_{max} to the cochlea (on average, 4 Gy less with conventionally fractionated regime and 6 Gy less with hyperfractionated RT) as well as a steeper dose gradient, resulting in lower cochlear volume at the high radiation dose compared to 2D and Sliding Window techniques (Table 1). These advantages are based on differences in the physical characteristics of the tomotherapy technique compared with conventional treatment technologies (described in detail in the Supplemental Data). More precise delineation of the cochlea in tomotherapy patients was achieved by using superior imaging modalities in treatment planning: a thickness of 1 mm between CT scans was used compared to 3 to 5 mm in patients treated with combined technique. This resulted in smaller cochlear volumes in tomotherapy plans compared to conventional and Sliding Window techniques. The smaller cochlear volume can potentially result in a cochlear-sparing dose distribution in the radiation plans. The influence of radiation position on dose distribution within the cochlea remains uncertain. According to Bohne et al. [31], the basal turn of the cochlea is responsible for high-frequency hearing and might be more sensitive to radiation than the organ of Corti, localized in the apical turn of the cochlea. We propose that the basal turn of the cochlea is less involved at the high dose in tomotherapy using the supine position compared to combined treatment using the prone position. This could explain the milder hearing impairment experienced preferentially at higher frequencies (6 kHz BCT, 8 kHz ACT) in tomotherapy patients compared to patients treated with combined technique. Because defining the cochlear substructures is complicated in actual treatment-planning images, it limits analyses of dose distribution within specific cochlear parts and therefore, determination of their individual role in the development of SNHL. Finally, Huang et al. [20] suggested that IMRT delivers a lower dose per fraction to the cochlea, with a probable decrease in biologic effect to the organ compared to conventional RT. This phenomenon can potentially lead to superior hearing outcomes in tomotherapy patients as is seen in patients after treatment with combined RT, where the craniospinal axis was irradiated with conventional RT.

A tendency towards a lower incidence of HL in all speech frequencies following tomotherapy was demonstrated (Fig. 2). Severe ototoxicity (≥40 dB at 0.5–3 kHz) was observed in 8.9% in the CRT group and 16.9% in the HRT group, which is less than the 18.2% observed by Paulino et al. [1] in medulloblastoma patients. Polkinghorn et al. [32] obtained grade 3 and 4 ototoxicity in only 13% of medulloblastoma patients, though this was focused on a shorter-term follow-up period of 12 months. Hua et al. [13] found SNHL in low frequencies (250 Hz–1 kHz) in 16% of children with brain tumor who received a cochlear D_{mean} of 55 Gy. A cumulative HL incidence of 26.1% and 13.4%, respectively, was found by Bhandare et al. [12] after combined radiochemotherapy and cranial RT alone in patients with head-and-neck cancer. Direct comparison of our data with results investigating different tumor entities or adults is, however, complicated due to the use of different therapy schemes with different cumulative radiation and/or cisplatin doses, and the possible impact of age on hearing impairment.

Current cochlear radiation dose constraints, including D_{mean} values, do not consider the additional detrimental effect of cisplatin on hearing thresholds. Many studies suggest that the first changes in high-frequency hearing thresholds are only found when the D_{mean} exceeds 45 Gy [9, 14, 17, 33–35]. We observed clinically relevant changes in high-frequency HL (8 kHz ACT >40 dB HL) in 30% of ears in the CRT group correlating with a D_{mean} <45 Gy for both radiation techniques. Reduction in the recommended cochlear dose objective in radiation treatment plans for medulloblastoma patients (e. g., D_{mean} reduction to 40 Gy) should be considered.

The effect of fraction dose has been analyzed in detail by Bhandare et al. [12] and by Lannering et al. [27]. Thus, Bhandare et al. reported no effect of fraction dose on the incidence and severity of SNHL in patients with head and neck tumors, although the median time period for persistent hearing alterations was found to be longer for CRT than HRT (2.1 years vs. 1.45 years). We found no significantly higher incidence of high-frequency SNHL in the CRT group than the HRT group. No impact on the severity of HL was found between these groups despite the lower mean cochlear dose in the CRT group (Fig. 2). This outcome may be explained by the higher total cisplatin dose applied in patients treated with conventional RT compared to hyperfractionated RT (Table 1).

Total dose of cisplatin has been shown to correlate with degree of HL in higher speech frequencies [1, 8–12, 16, 19, 34–36]. We observed bilateral, symmetrical change in hearing thresholds in the mid and high frequencies in 90% of patients at a total cisplatin dose above 210 mg/m². This finding is in agreement with the results of Schell et al. [16] who found clinically relevant substantial HL in irradiated patients with a cumulative cisplatin dose above 270 mg/m². In contrast, Paulino et al. [1] found no correlation between total cisplatin dose and the severity of ototoxicity in medulloblastoma patients. The authors explained this finding by reporting that cisplatin dose was reduced if high-grade ototoxicity (grade 3) occurred. Broad interindividual susceptibility to cisplatin-induced ototoxicity has been reported in the literature: no HFHL following 360–480 mg/m² in some children but significant HFHL following 120 mg/m² in others [37, 38]. This discrepancy in audiological outcome during cisplatin therapy presumes individual susceptibility to the drug. Cisplatin ototoxicity was found by Kretschmar et al. [36] to be sequence dependent, as demonstrated in 39 pediatric patients with malignant brain tumors, with no increase in HL after RT if cisplatin was given before RT (follow-up over 5 years).

Interestingly, the worst hearing threshold in the present study was found 8–12 months after RT for both radiation techniques and fractionation regimes, despite the HRT and CRT groups having different total cisplatin doses. Further improvement of mid- and high-frequency hearing thresholds up to the latest follow-up was observed in all patients treated with tomotherapy (Fig. 4). Thus, the use of IMRT/image-guided (IGRT) techniques, such as tomotherapy, contributes to the optimization of dose distribution within the cochlea, and, correspondingly, to the reduced synergistic detrimental effect on the cochlea by the combination with cisplatin.

Conclusion

For patients who receive simultaneous cisplatin-based chemotherapy, the cochlear radiation dose should be kept as low as possible. Cochlear D_{mean} was found to have a linear correlation with the incidence and severity of hearing impairment. The risk of clinically relevant HL becomes evident when D_{mean} exceeds 45 Gy independent of radiation technique or radiation regime. The total dose of cisplatin was found to correlate with the degree of HL, demonstrating a bilateral change in hearing thresholds in the mid and high frequencies at a total dose above 210 mg/m².

Compliance with ethical guidelines

Conflict of interest S. Scobioala, R. Parfitt, P. Matulat, C. Kittel, F. Ebrahimi, H. Wolters, A. am Zehnhoff-Dinnesen and H.T. Eich declare that they have no competing interests.

Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors.

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