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ORIGINAL ARTICLE

Age-corrected hearing loss after chemoradiation in cervical cancer patients

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Abstract

Objective This study aimed to evaluate subjective and objective hearing loss in cervical cancer patients after chemoradiation with cisplatin (mono).

Patients and methods A total of 51 cervical cancer patients with indication for chemoradiation were included. Pure tone and impedance audiometry were performed before and after chemoradiation. Hearing loss was scaled according to ASHA criteria. Subjective hearing was assessed with the Oldenburger Sentence Test. To consider age-dependent changes, hearing loss was corrected for age and the time interval between measurements.

Results Median age at diagnosis was 46 years, 46% were active/former smokers ($n=24$), 28 (54%) patients were never-smokers. Median total weekly cisplatin dose was 70 ± 14.2 mg. Cumulative doses of cisplatin during chemoradiation ranged between 115.2 and 400 mg cisplatin (mean 336.1 mg, median 342 ± 52.7 mg). The median interval between last chemotherapy and second audiometry was 320 ± 538 days (35–2262 days). Changes in hearing threshold ≥20 dB were experienced by 32/52 patients (62%) following chemoradiation, 55% of them for frequencies ≥6000 Hz. No statistically significant hearing loss remained after chemoradiation upon correction for age and time interval. Patients >40 years had a higher risk of hearing loss than younger patients. Objective data on hearing function did not correlate with subjective hearing loss and did not impair daily activity in any patient.

Conclusion Chemoradiation with cumulative cisplatin doses up to 400 mg did not lead to significant impairment of objective or subjective hearing. For cervical cancer patients undergoing chemoradiation, standard audiometry is not indicated.

Keywords Audiometry · Cisplatin · Risk factors · Quality of life · Hearing loss, sensorineural

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Alterskorrigierter Hörverlust nach Radiochemotherapie bei Patientinnen mit Zervixkarzinom

Zusammenfassung

Hintergrund Ziel der Arbeit war, bei Patientinnen mit Zervixkarzinom vor und nach kombinierter Radiochemotherapie mit Cisplatin (mono) den subjektiven und objektiven Hörverlust zu ermitteln.

Patienten und Methoden Eingeschlossen wurden 51 Zervixkarzinom-Patientinnen mit einer Indikation für eine kombinierte Radiochemotherapie. Die Tonschwellenaudiometrie erfolgte vor und nach Radiochemotherapie. Diese wurde nach ASHA-Kriterien dokumentiert. Die subjektive Hörminderung wurde mit dem Oldenburger Inventar erfasst. Die Daten wurden entsprechend dem Abstand zwischen erster und zweiter Messung auf der Basis des zu erwartenden Hörverlusts einer Normalpopulation alterskorrigiert.

Ergebnisse Das mediane Alter bei Diagnose betrug 46 Jahre; 46 % ($n=24$) waren aktive/ehemalige Raucherinnen, 54% ($n=28$) Nieraucherinnen. Mediane absolute Wochendosen waren 70 mg ± 14,2 mg Cisplatin. Kumulative Absolutdosen betrugen 115,2–400 mg Cisplatin, im Mittel 336,1 mg (342 mg ± 52,7 mg). Das mediane Intervall zwischen letzter Chemotherapie und zweiter Audiometrie war 320 ± 538 Tage (Spanne 35–2262 Tage). Nach Radiochemotherapie zeigten 32/52 Patientinnen (62 %) Veränderungen der Hörschwelle ≥20 dB, davon 55 % bei Frequenzen ≥6000 Hz. Korrigiert nach Alter bzw. Zeitintervall zwischen den Messungen ergab sich jedoch kein statistisch signifikanter Unterschied im Vorher-Nachher-Vergleich. Patientinnen >40 Jahre hatten im Vergleich zu jüngeren Patientinnen ein höheres Risiko für eine Hörminderung. Die objektiven Daten zur Hörfunktion korrelierten nicht mit den subjektiven Angaben zum Hörverlust und beeinträchtigten bei keiner Patientin den Alltag.

Schlussfolgerung Die kombinierte Radiochemotherapie mit kumulativen Cisplatindosen bis 400 mg führte in der objektiven und subjektiven Wahrnehmung der Patientinnen zu keiner statistisch signifikanten Hörminderung. Für die beschriebene Patientenkohorte ist eine Tonaudiometrie nicht indiziert.

Schlüsselwörter Audiometrie · Cisplatin · Risikofaktoren · Lebensqualität · Sensorineuraler Hörverlust

In 1965, Rosenberg et al. [1] described that platinum compounds inhibit cell division in *Escherichia coli*. Since the new millennium, cisplatin (cis-diamminedichloridoplatinum, CDDP)-based chemoradiation and brachytherapy have become the standard of care for cervical cancer treatment [1]. However, CDDP has a number of dose-limiting side effects including nephrotoxicity, ototoxicity, neurotoxicity, and hematotoxicity. Serum platinum levels are still elevated >20 years after treatment because of incomplete renal elimination [2–12]. Platinum-induced ototoxicity may manifest as bilateral, progressive, and irreversible sensorineural hearing loss with significant impact on quality of life, healthcare costs, and productivity [13, 14].

The molecular mechanisms of cisplatin ototoxicity include reactive oxygen species causing oxidative damage of nucleic acids. The organ of Corti is most sensitive to cisplatin exposure, with apoptotic degeneration of the hair cell resulting in a concentration-dependent loss of outer hair cells within 2 days following CDDP [15, 16]. Furthermore, it resulted in a long-term susceptibility to hearing loss after cisplatin treatments. Noise and ototoxic drugs such as aminoglycoside may enhance the effect [17]. An initial elevation of high-frequency audiometric thresholds, followed by a progressive loss into the lower frequencies with continued therapy has been demonstrated [18].

Age at the time of chemotherapy, serum cisplatin levels and the cumulative dose of cisplatin, number and duration of chemotherapy cycles, and the method of application, as well as gender and glutathione S-transferase gene polymorphisms correlate with the reported toxicity [17, 19]. However, the inter-individual variability of ototoxicity is profound and a generally accepted grading system among oncologists is still lacking. This is complicated by the fact that in the majority of investigations on CDDP-related hearing loss, CDDP had been combined with other chemotherapies and/or direct radiation of the vestibulocochlear organ [13, 14, 20–25]. Only a few investigations report on the effect of cisplatin applied as monotherapy [26].

Therefore, all adult patients before planned cisplatin-containing chemotherapy or radiochemotherapy should receive audiometric testing to monitor the occurrence of cisplatin-induced hearing loss [20, 21, 23, 27]. Audiologic examination at higher frequencies >8000 Hz has been shown to be more sensitive than testing ≤8000 Hz [28].

In the majority of investigations on CDDP-related hearing loss, CDDP was combined with other chemotherapies and/or radiation [19, 29]. Ototoxicity is usually detected when a communication problem becomes evident [26]. Although prospective audiologic evaluations remain the only reliable means for detecting ototoxicity before it becomes symptomatic, even in developed countries, this has not become part of the standard follow-up schedule after cancer treatment [30].

The intention of this study was to evaluate objective hearing loss in correlation with patient-reported hearing outcome in a mono-institutional cohort of patients with proven cervical cancer after cisplatin-based (mono) primary or adjuvant chemoradiation. A further aim was to assess whether routine hearing testing in cervical cancer patients undergoing standard chemoradiation is still necessary.

Materials and methods

After ethical approval, 51 patients with histologically proven cervical cancer with an indication for primary or adjuvant chemoradiation were included. Patients participating in the study had no prior history of significant hearing difficulties or noise exposure. All patients had normal renal function with a filtration rate of at least 60 ml/h. No patient showed evidence of metastatic disease (except histologically proven para-aortic lymph node metastases, $pM1_{Lym}$), nor had they undergone radiotherapy to the head and neck region or temporal bone. The International Federation of Gynecology and Obstetrics (FIGO) stages of the 51 patients were IA ($n=2$), IB ($n=16$), IIA ($n=3$), IIB ($n=23$), IIIA ($n=1$), IIIB ($n=6$), and IVB ($pM1_{LYM}$, $n=1$). Indications for primary chemoradiation were histologically confirmed pelvic and/or para-aortic lymph nodes and/or locally advanced disease (≥FIGO IIB) or a combination of intermediate risk factors (lymphovascular space involvement=LSVI+, Grading G3, age <40 years, bulky disease).

Chemoradiation

For radiation planning, patients underwent a CT in supine position using immobilization devices ("kneefix" and "footfix," Unger®, Mülheim-Kärlich, Germany) with 2 mm slices and i. v. contrast medium with a full bladder and an emptied rectum from the first lumbar vertebra to the trochanter minor. In patients with histologically confirmed lymph node metastases in the para-aortic region, planning CT was extended up to the renal vessels.

The prescribed dose was 1.8-Gy single fractions to a total dose of 50.4 Gy to the planning target volume (PTV_A). The integrated boost was given to the parametric region, defined on anatomic landmarks and titanium markers during the laparoscopic staging procedure plus a 0.8–1 cm margin (=PTV_B) with 2.12 to 59.36 Gy in 28 fractions. MRI-guided intracervical brachytherapy was performed with five single fractions to a nominal total dose of 25 Gy covering the residual tumor on MRI at the time of starting brachytherapy. Patients were treated either with volumetric arc therapy (VMAT) with 6-MV photons on a linear accelerator (DHX; Varian®, Palo Alto, CA, USA) or using helical tomotherapy (Tomotherapy; Accuray®, Sunnyvale, CA, USA) with 6-MV photons and daily image guidance. Chemotherapy consisted of 40 mg/m² body surface cisplatin for five weekly applications.

Audiometric testing

Baseline pure tone audiometry both for air conduction and bone conduction was performed at 250, 500, 1000, 2000, 4000, and 8000 Hz along with impedance audiometry before and after completion of the chemoradiation (audiometry system Dorn AT335, Version 6.50, and AT900; Auritec®, Hamburg, Germany). Ototoxicity was measured using intra-individual audiogram comparisons [15, 17]. Corrections due to the expected age-related physiological hearing loss in healthy subjects were performed for all patients [31, 32].

ASHA criteria

The international American Speech-Language-Hearing Association (ASHA) criteria define hearing loss as a hearing threshold at any frequency (0.25 to 12 kHz) that exceeds 20 dB for either ear. ASHA criteria define hearing loss severity as mild: 21 to 40 dB; moderate: 41 to 55 dB; moderately severe: 56 to 70 dB; severe: 71 to 90 dB; and profound: 90 dB; for at least one tested frequency for either ear [33].

Patient-reported outcome

Patients completed questionnaires concerning the impact of self-reported symptoms on quality of life. A validated questionnaire (Oldenburg Sentence Test) was used to quantify the patient-reported hearing function and their impairment in daily life. Twelve standardized questions had to be answered, with maximum five points per question. A maximum total of 60 points could be reached (best possible result) [33–36]. Missed answers were corrected by a correction factor of reached points/given answers × 60.

Statistics

Descriptive analyses included means, medians, standard deviations, and ranges for quantitative measurements as well as absolute frequencies and percentages for categorical variables. For each of the frequencies and separately for the left and right ear, the null hypothesis "no hearing loss" was tested vs. the alternative hypothesis "hearing loss" using the two-sided *t*-test with type-one error 0.05 (two-sided) and no correction for multiple testing. In addition to the raw differences, corrected differences of hearing thresholds using data of age-related hearing loss were tested. This was done

by calculating the time interval between the first and second audiometry and the expected hearing loss—which also depended on patients age—according to Gablenz and et al. and Holube et al. for each subject [37, 38]. This expected loss was then subtracted from the observed loss to get the correct difference.

Results

Median age at diagnosis was 46 years (range 24–74 years). Regarding smoking status, 24 patients (46%) were active or former smokers, while 28 (54%) patients were non/never-smokers. The median total administered weekly cisplatin dose was 70 ± 14.2 mg. Cumulative doses of cisplatin during chemoradiation ranged between 115.2 and 400 mg, with a mean dose of 336.1 mg (median 342 ± 52.7 mg). All patients completed the radiation protocol.

Audiometry was performed before and after chemoradiation. The median interval between last chemotherapy and second audiometry was 320 ± 538 days (35–2262 days). Changes in hearing threshold of ≥20 dB were experienced by 32/52 patients (62%) following chemoradiation, 55% of them for frequencies ≥6000 Hz. For frequencies of 6 and 8 kHz, differences in hearing threshold were 2.90 versus 5.1 dB for the right ear and 3.50 and 4.12 for the left ear, respectively (Fig. 1). Considering the different intervals between last chemotherapy application and hearing test, a correction was made for expected overlapping age-related hearing loss, which might also be independent from cisplatin [37]. After adjustment for an age/time effect between both audiometries, there were no statistically sig-

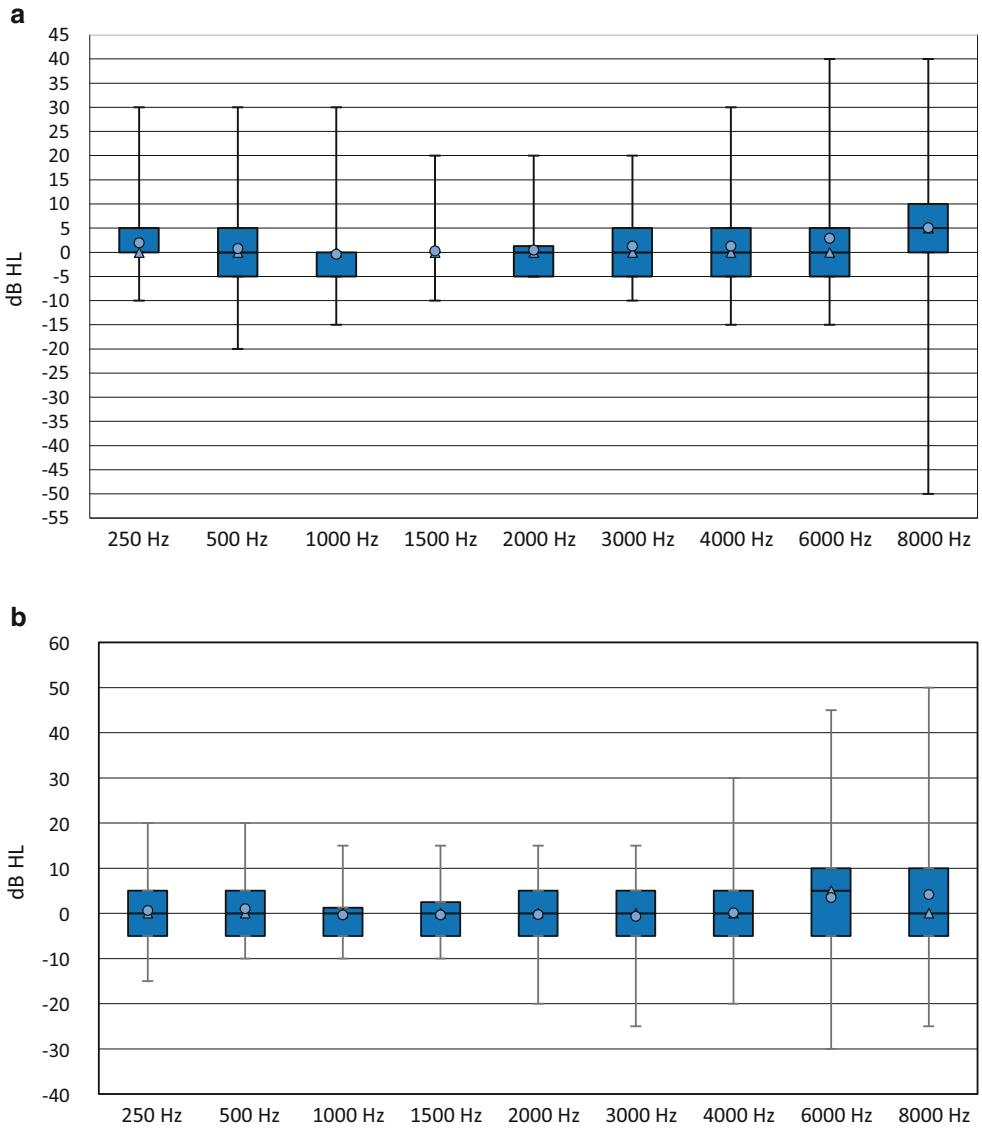

Fig. 1 **a** Difference in hearing threshold (dB) of the right ear. **b** Difference in hearing threshold (dB) of the left ear. *HL* hearing level, with standard deviation (*blue blocks*), mean (*circles*) and median (*triangles*)

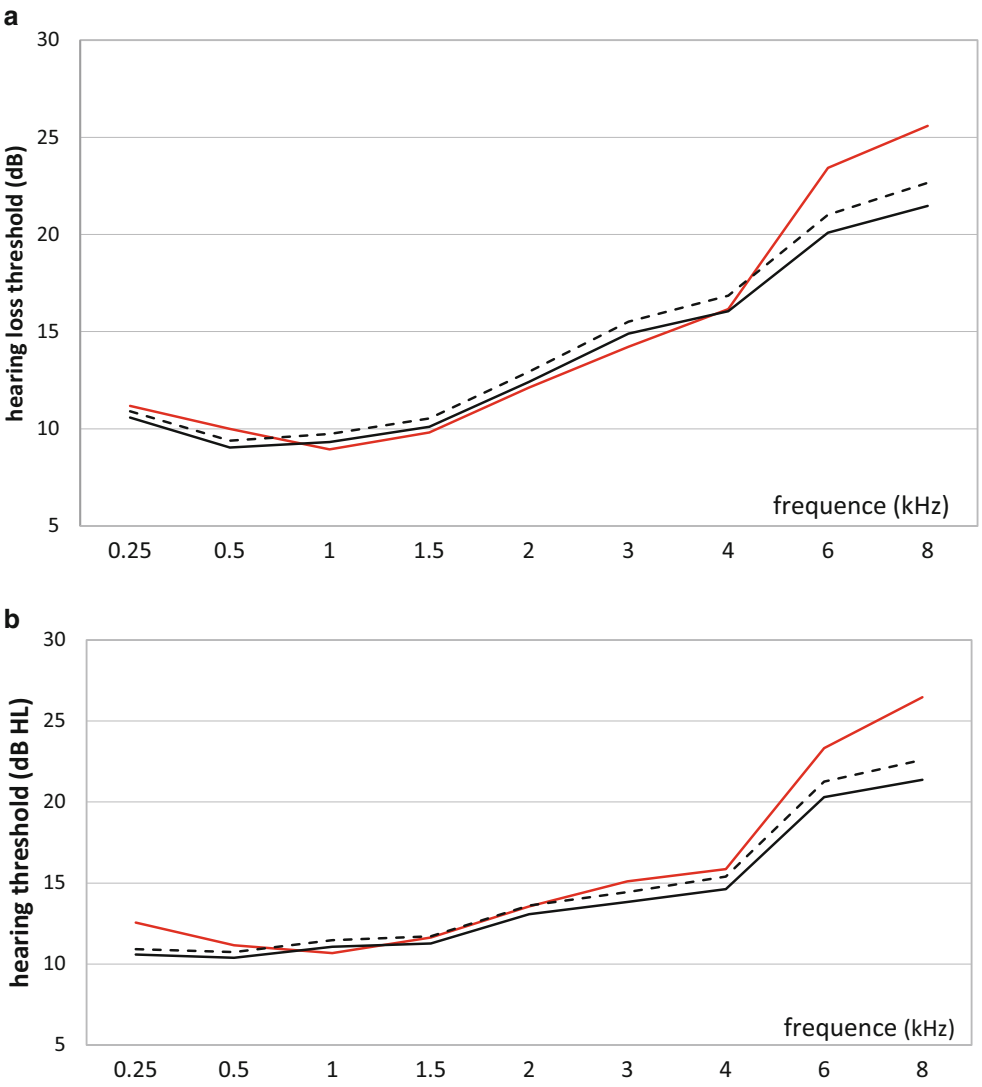

Fig. 2 **a** Hearing threshold (dB HL) for frequencies (0.25–8 kHz) before chemoradiation (*black*), after chemoradiation (*red*), and expected hearing after adjustment for time (*dashed line*, interval between treatment and testing) for the left ear. **b** Hearing threshold (dB HL) for frequencies (0.25–8 kHz) before chemoradiation (*black*), after chemoradiation (*red*), and *dashd line* with expected hearing after adjustment for time (interval between treatment and testing) for the right ear. *HL* hearing level

nificant differences between pre- and post-chemotherapy measurements (Fig. 2; Table 1 and 2) at 6 and 8 MHz.

According to the World Health Organization (WHO) classification [37] there was an increasing hearing loss in 2 patients, from grade 0 to grade 2 and from grade 0 to grade 1 for the left and right ears, respectively. With regard to cisplatin dose and smoking status of the patients, there was no correlation with the degree of hearing loss ($P = 0.63$; $P = 0.84$). Patients >40 years were at higher risk for hearing loss than younger patients. The percentage of patients with hearing impairment increased from 20% among the patients aged 20–30 years to 50% of the patients >60 years. With regard to the ASHA criteria, 19/52 (36%) patients experienced a significant hearing loss. Adjusted for age, in only 7/52 patients (13%) could a hearing loss according to ASHA criteria be documented.

The Oldenburg questionnaire was completed by 47 patients. The reported minimum and maximum points were 30/60 and 60/60, respectively, with a median of 56 ± 6 points. The majority of patients reached 50/60–60/60 points. These results correlate with threshold differences of ±5 dB (Fig. 3). Of note, self-reported hearing impairment and hearing loss in dB after chemoradiation did not have any relevant influence for daily activity in any patient.

Discussion

Depending on dose, genetic determination, and several patient-related factors, cisplatin may cause permanent bilateral sensorineural hearing loss in substantial numbers of patients. Data indicate that the damage to the hearing system is permanent [39]. Cranial irradiation (base of skull) can worsen this irreversible hearing loss [29]. However, most clinical protocols contain a combination of cisplatin and at least one more cytotoxic drug [28, 40–42], a combination with other neurotoxic agents [14, 40, 42, 43], and/or

Table 1 Age-adjusted mean differences in hearing loss (dB) pre- versus post chemoradiation for the right ear for the tested frequencies 0.25–8 kHz

Right ear				
Frequency	Mean difference	Confidence interval		Significance level
(kHz)	(dB)	Upper	Lower	*P*-value
0.25	1.63569	3.6824	–0.4110	0.115
0.5	0.41694	2.3600	–1.5262	0.668
1	–0.79090	0.8521	–2.4339	0.338
1.5	–0.14120	1.3603	–1.6427	0.851
2	–0.05391	1.2968	–1.4046	0.936
3	0.65835	2.3881	–1.0714	0.448
4	0.45978	2.6705	–1.7509	0.678
6	1.94737	4.6043	–0.7096	0.147
8	3.86704	7.8709	–0.1369	0.058

Table 2 Age-adjusted mean differences in hearing loss (dB) pre- versus post chemoradiation for the left ear for the tested frequencies 0.25–8 kHz

Left ear				
Frequency	Mean difference	Confidence interval		Significance level
(kHz)	(dB)	Upper	Lower	*P*-value
0.25	0.27476	2.2920	–1.7425	0.786
0.5	0.60925	2.2440	–1.0255	0.458
1	–0.79090	0.6815	–2.2633	0.286
1.5	–0.82748	0.5272	–2.1821	0.226
2	–0.82314	0.8918	–2.5381	0.340
3	–1.30243	0.7542	–3.3591	0.209
4	–0.69406	1.6681	–3.0562	0.558
6	2.58333	6.3044	–1.1378	0.169
8	2.92976	6.4912	–0.6317	0.105

a radiation treatment to the head and neck region or base of skull [44].

For patients undergoing chemoradiation for head and neck malignancies, multivariate analysis indicated that cumulative cisplatin dose, radiation-induced secretory otitis media, and the dose to 0.1 cc ($D_{0.1cc}$) to the cochlea are factors predicting sensorineural hearing loss [45]. Antioxidants have shown efficacy in preventing ototoxicity in animal models and patients [46] but have not found entrance into clinical practice. It is possible that genomic analysis may eventually be able to identify patients susceptible to ototoxicity in the future. However, a routine hearing test is currently recommended for all patients in whom platinum-based chemoradiation is planned. Various methods for reporting platinum-induced ototoxicity, including the National Cancer Institute (NCI) criteria, Brock's grading system, the ASHA criteria, the WHO criteria, the Pediatric Oncology Group (POG) criteria, and many others have been published [43, 47, 48] and are used internationally, thus making comparisons between studies difficult [15].

The aim of the present analysis was to evaluate the need for routine ototoxicity monitoring in the context of chemoradiation in a cohort of homogeneously treated cervical cancer patients with cisplatin mono [34].

There is a wide range of reported hearing loss in patients with different tumor entities. Bokemeyer described hearing loss in 66% of the patients by testing frequencies of 0.5 to 8 kHz at a median of 4.8 years after cisplatin-based chemotherapy [34, 38, 49]. In patients with head and neck cancer undergoing chemoradiation, Jain et al. [20] reported hearing loss in 27.5, 72.5, and 82.5% at 2, 4, and 8 kHz, respectively. The higher rates of hearing loss are due to radiation of the head and neck region, even with outdated radiation techniques. In a national multicenter follow-up survey from 1998 to 2002, 1814 patients treated for testicular cancer in Norway during the period 1980–1994 participated. Hearing impairment was objectively assessed by audiometry at 4000 Hz in 755 men. About 20% reported hearing impairment and tinnitus as major symptoms [26]. Frisina et al. tested 488 patients with testicular cancer: 20% had severe or profound hearing loss, a level at which hearing aids are typically recommended. An additional 37% of patients with moderate or moderately severe ASHA-defined hearing loss would benefit from additional audiologic follow-up, as clinically indicated [50].

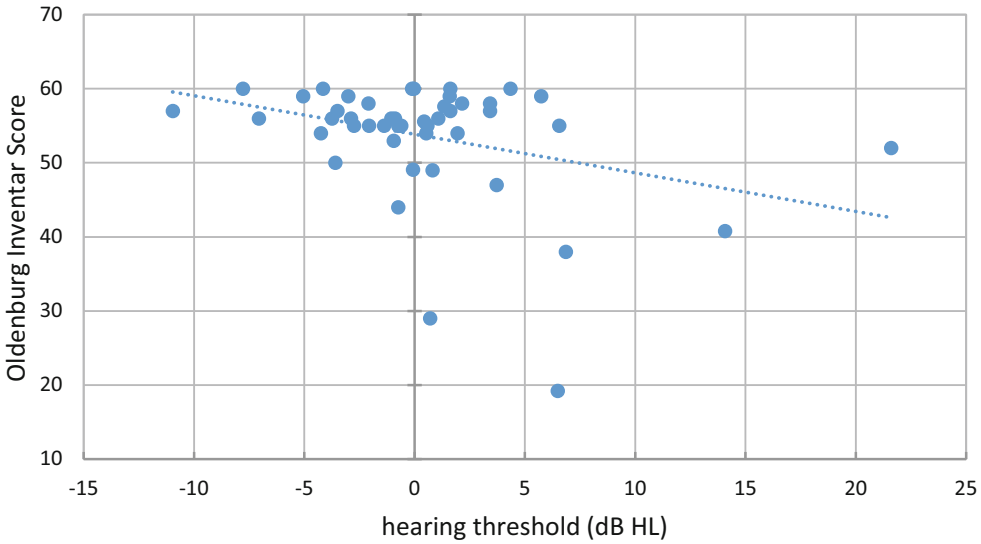

Fig. 3 Hearing threshold differences (all frequencies) and correlation with the reported Oldenburg questionnaire scores. Trend toward hearing loss and self-reported impairment (*dotted line*)

In our cohort, 32/52 patients (62%) experienced changes in hearing threshold of ≥20 dB after chemotherapy, 55% of them for frequencies ≥6000 Hz. Numerical differences between the median values pre- and post-chemotherapy were ≤5 dB, which is comparable to other publications [42]. As reported by other authors, hearing loss was predominantly bilateral, symmetrical, and above the speech range [14]. This is reflected by the patient-reported outcome within the questionnaire.

According to the WHO classification [51, 52] there was an increasing hearing loss in only 2 patients of the current study. With regard to the ASHA criteria, 36% of our cohort experienced a significant hearing loss, which is less than the evaluation by objective measurement.

Unnoticed by many authors, hearing is a physiological function dependent on genetics, age, and lifestyle. The risk of developing hearing loss appeared significant for children and patients >42 years [39]. In our study, we present non-selected patients with a wide range of age and a median age >40 years.

Age-dependent changes in adult patients have to be considered for interpretation of the findings for various reasons: there are physiological changes during a person's lifetime that depend on genetics and lifestyle [22, 41]. After cisplatin application, the maximum value of hearing loss after chemotherapy can be underestimated if the test is performed very early or overestimated if the test is done years later because of progressive hearing loss after chemotherapy and overlapping effects of age and lifestyle. Therefore, we used age- and gender-specific corrections to generate a valid approximation of the expected hearing function at the time of testing and to compensate for the different timepoints of measurement in our patients [35].

In our patient cohort, after adjustment for age and time interval between the two audiometries, no significant changes remained in audiologic measurement, WHO grading, or ASHA criteria upon comparing pre- and post-chemotherapy hearing function. One possible explanation is that CDDP-induced presbycusis usually affects higher frequencies and is not significant for routine speech. Only one publication demonstrated that a significant hearing loss resulted at low (750 Hz) and high frequencies (6000 and 8000 Hz; [32]). Furthermore, the degree of hearing loss is related to the dose. With increasing cumulative doses from 400 to 600 mg, there is a doubled risk for grade 3 and 4 ototoxicity [51]. The reported cumulative doses of cisplatin differ considerably, between 200–800 mg/m² [22, 40]. With a mean dose of 336 mg cisplatin, the dose was below the level of 400 mg. As expected, we could not demonstrate any grade 3 or 4 ototoxicity [14, 17, 40, 42].

Subjective hearing loss has been reported by several authors. Because of different questionnaires and evaluation systems and/or small numbers of patients, the comparability with our data is limited [27, 42, 53]. Subjective hearing loss was reported by 27% of cases with less differentiated questionnaires [14]. Using combined audiometric and self-reported observations, Bokemeyer et al. documented clinically relevant hearing difficulties in 21% of patients [14]; Oldenburg et al. [20] reported that 24% of 238 patients answered "Quite a bit" or "Very much."

As in our patients, the measured hearing loss did not correlate with the patients' subjective impression. While 70% of patients who had received cisplatin had an absolute hearing threshold of 25 dB at 8000 Hz, only 8% of patients reported hearing difficulties, although this figure was almost double that reported for patients without chemotherapy [36].

One drawback of the present cohort is that the testing did not cover frequencies >8000 Hz, as in many other publications [44]. It can be speculated that had we used even

higher frequencies for testing, we could have demonstrated significant changes [14, 40, 43, 54]. Fausti et al. noticed that only 37% of the patients with initial changes can be detected within the conventional frequencies, whereas monitoring higher frequencies would have allowed identification of 88% of patients with initial changes [19, 29].

With regard to infusion time and the ototoxic risk, there is only one randomized trial in children with neuroblastoma. A review of data summarized that there is "no evidence of effect" which is not the same as "evidence of no effect" of the correlation of infusion time with ototoxicity [30, 42]. We used a once weekly 30–60 min infusion schedule for all our patients and therefore could not detect differences in tolerability with regard to application schedule. In animals, a continuous low-dose cisplatin application caused less ototoxic effects compared with bolus application [55]. The question of whether alternative schedules (e.g., 20 mg/m^2 cisplatin days 1–5 first and fifth week) are less toxic in humans remains open.

The major strength of the current study is the homogenous administration of chemoradiation within the entire cohort. To our knowledge, this is the largest study of cisplatin-associated ototoxicity in survivors after chemoradiation in cervical cancer including quantitative comparisons of frequency-specific audiometric findings, WHO grading, and ASHA criteria with patient-reported outcomes and adjustment for age. Weaknesses are different time intervals between the first and second audiogram, and missing data for very high frequencies.

Conclusion

Patients with cervical cancer who underwent primary or adjuvant chemoradiation with cumulative cisplatin cumulative doses ≤400 mg did not experience statistically significant hearing loss in the speech frequencies. If larger studies confirm these findings, routine use of pre- and post-chemotherapy audiologic evaluation can be avoided in these patients, but might still be considered in patients with specific professions (teachers, singers, etc.) or pre-existing hearing loss. Patients should be informed about the higher susceptibility of the inner ear for noise.

Conflict of interest S. Marnitz, L. Schermeyer, S. Dommerich, C. Köhler, H. Olze, V. Budach, and P. Martus declare that they have no competing interests.

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