



Unilateral cochlea sparing in locoregionally advanced head and neck cancer: a planning study

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Abstract

Background Cochlea sparing can reduce late ototoxicity in head and neck cancer patients treated with cisplatin-based radiochemotherapy. In this situation, a mean cochlear dose (MCD) constraint of 10 Gy has been suggested by others based on the dose–effect relationship of clinical data. We aimed to investigate whether this is feasible for primary and postoperative radiochemotherapy in locoregionally advanced tumors without compromising target coverage.

Patients and methods Ten patients treated with definitive and ten patients treated with adjuvant intensity-modulated radiotherapy (IMRT) and concurrent chemotherapy were investigated. The cochleae and a planning risk volume (PRV) with a 3 mm margin were newly delineated, whereas target volumes and other organs at risk were not changed. The initial plan was recalculated with a constraint of 10 Gy (MCD) on the low-risk side. The quality of the resulting plan was evaluated using the difference in the equivalent uniform dose (EUD).

Results A unilateral MCD of below 10 Gy could be achieved in every patient. The mean MCD was 6.8 Gy in the adjuvant cohort and 7.6 Gy in the definitive cohort, while the non-spared side showed a mean MCD of 18.7 and 30.3 Gy, respectively. The mean PRV doses were 7.8 and 8.4 Gy for the spared side and 18.5 and 29.8 Gy for the non-spared side, respectively. The mean EUD values of the initial and recalculated plans were identical. Target volume was not compromised.

Conclusion Unilateral cochlea sparing with an MCD of less than 10 Gy is feasible without compromising the target volume or dose coverage in locoregionally advanced head and neck cancer patients treated with IMRT. A prospective evaluation of the clinical benefit of this approach as well as further investigation of the dose–response relationship for future treatment modification appears promising.

Keywords Organs at risk · Toxicity · Radiotherapy, Intensity-Modulated · Cisplatin · Ear, inner

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Einseitige Schonung der Cochlea bei lokal fortgeschrittenen Kopf-Hals-Tumoren: eine Planungsstudie

Zusammenfassung

Zielsetzung Eine Schonung der Cochlea kann die Toxizität bei Patienten mit Kopf-Hals-Tumoren, die mit einer cisplatinbasierten Radiochemotherapie behandelt werden, senken. Eine prospektive klinische Studie errechnete eine mittlere cochleäre Dosis (MCD) von <10Gy, die in der kombinierten Therapie maximal appliziert werden darf. Wir untersuchen, ob dies sowohl bei primär radiochemotherapierten als auch bei postoperativ radiochemotherapierten Kopf-Hals-Tumorpatienten möglich ist, ohne dass es zu Unterdosierungen im Zielgebiet kommt.

Patienten und Methoden Bei 10 Patienten, die eine definitive Radiochemotherapie, und bei 10 Patienten, die eine adjuvante intensitätsmodulierte Radiotherapie (IMRT) und eine gleichzeitige Chemotherapie erhielten, wurden die Bestrahlungspläne unter der Prämisse einer einseitigen MCD <10Gy neu berechnet. Hierfür wurde die Cochlea an sich sowie mit einem 3-mm-Saum („planning risk volume“, PRV) neu skizziert; andere Risikoorgane und das Zielvolumen wurden nicht verändert. Die Qualität der resultierenden Bestrahlungspläne wurde nach dem Konzept der „equivalent uniform dose“ (EUD) evaluiert.

Ergebnisse Eine einseitige MCD <10Gy wurde in allen Fällen erzielt. Die MCD lag bei 6,8Gy in der adjuvant therapierten und bei 7,6Gy in der definitiven Kohorte. Die MCD der nichtgeschonten Cochleae wies 18,7Gy bzw. 30,3Gy auf. Die mittlere PVR-Dosis betrug 7,8Gy bzw. 8,4Gy der geschonten Cochleae und 18,5Gy bzw. 29,8Gy der Gegenseite. Die mittlere EUD der neu berechneten und der ursprünglichen Pläne waren identisch.

Schlussfolgerung Eine einseitige Cochleaschonung mit einer MCD <10Gy ist mit der IMRT möglich, ohne das Zielvolumen in fortgeschrittenen Kopf-Hals-Tumorpatienten zu kompromittieren. Eine prospektive Studie, die die Dosis-Wirkungs-Beziehung und den klinischen Benefit dieses Ansatzes näher untersucht, scheint vielversprechend.

Schlüsselwörter Risikoorgane · Toxizität · Intensitätsmodulierte Radiotherapie · Cisplatin · Innenohr

Locoregionally advanced squamous cell carcinoma of the head and neck region (HNSCC) is usually treated with curative radiochemotherapy or surgery and adjuvant radio- or radiochemotherapy. Parallel cisplatin has become the standard chemotherapy [31]. With this approach, a substantial proportion of these patients are cured, making long-term toxicity an increasingly relevant topic. While some late toxicities such as xerostomia and dysphagia have been studied extensively [10, 39], there is a paucity of data concerning late inner ear toxicity [2, 29]. Symptoms associated with inner ear toxicity (hearing loss or deafness, tinnitus, vertigo, and postural problems) are known to significantly reduce quality of life and socioeconomic status of the patients [4, 8, 24, 30, 41]. Both radiotherapy and cisplatin-based chemotherapy can alone cause inner ear toxicity. In general, most authors agree that the combination of radiotherapy and cisplatin is more ototoxic than a single-modality treatment [3, 15–17, 20, 25, 32, 38]. To date, there is no generally accepted radiation dose constraint that is known to be safe for application to the inner ear. The QUANTEC analysis [3] found mean cochlear doses (MCD) of 35–45 Gy to be associated with late ototoxicity, with parallel cisplatin reducing the tolerated dose. In this respect, Hitchcock et al. proposed an MCD constraint of 10 Gy when using combined radiochemotherapy based on the results of a clinical study [15]. So far, this dose constraint has not been prospectively validated. The first step towards implementing a clinical trial to investigate the effect of the upper

MCD limit of 10 Gy is to demonstrate that target volume coverage is not compromised. The purpose of our planning study was therefore to investigate whether it is feasible to achieve a unilateral MCD <10 Gy in both the definitive and the adjuvant radiochemotherapy setting without compromising the planning target volume or dose coverage, and without applying intolerably high doses to other organs at risk (OAR).

Patients and methods

We investigated 10 consecutive HNSCC patients with adjuvant radiochemotherapy and 10 consecutive patients with definitive radiochemotherapy (for characteristics, see Table 1). Patients with nasopharyngeal or laryngeal tumors were not included. All 20 patients had locoregionally advanced tumors and received bilateral neck irradiation with a simultaneous integrated boost with a Monte Carlo calculated volumetric modulated arc therapy (VMAT) approach (by Hyperion® [Tuebingen University, Tuebingen, Germany, in-house product]) in an individualized thermoplastic mask using a linear accelerator with 6 MV photons.

The cochlea was delineated in the 3 mm planning CT scans. Since ototoxicity might also be influenced by damage to other structures of the hearing apparatus, we additionally defined the vestibular organ, the auditory nerves, the middle ear, and the Eustachian tubes (for definition of

Table 1 Gender and tumor characteristics of study patients

Therapy	Gender	Grading	T stage	N stage	M stage	R	Dose (adjuvant/ boost)	Chemotherapy	Location primary
Adjuvant	m	Basaloid	2	N2b	0	2	54/70 Gy	cDDP/5-FU	Hypopharynx
	m	3	2	N1	0	0	54/64 Gy	cDDP/5-FU	Oropharynx
	m	2	3	N2b	0	0	54/64 Gy	cDDP/5-FU	Oropharynx
	m	2	2	N2b	0	1	54/64 Gy	cDDP/5-FU	Oro-/ hypopharynx
	m	2	4	N2b	0	1	54/66 Gy	cDDP/5-FU	Hypopharynx
	m	3	2	N2c	0	0	54/64 Gy	cDDP/5-FU	Oropharynx
	m	2	2	N0	0	1	54/64 Gy	cDDP/5-FU	Oropharynx
	m	2	4	N0	0	1	54/66 Gy	cDDP/5-FU	Hypopharynx
	f	Basaloid	2	N2b	0	1	54/66 Gy	cDDP/5-FU	Oropharynx
	m	2	4	N0	0	1	50.4/64 Gy	cDDP/5-FU	Oral cavity/ oropharynx
Definitive	m	3	4	N1	0	–	54/70 Gy	cDDP	Oropharynx
	f	2	2	N1	0	–	54/70 Gy	cDDP	Oropharynx
	m	3	3	N1	0	–	54/70 Gy	cDDP	Oro-/ hypopharynx
	m	3	3	N2b	0	–	54/70 Gy	cDDP	Oropharynx
	f	3	4	N2b	0	–	54/70 Gy	cDDP	Oro-/epipharynx
	m	3	2	N2b	0	–	54/70 Gy	cDDP	Oropharynx
	m	2	4	N2b	0	–	54/70 Gy	cDDP	Oropharynx
	m	2	4	N1	0	–	54/70 Gy	cDDP	Oropharynx
	m	2	4	N2c	0	–	54/70 Gy	cDDP	Oro-/ hypopharynx
	m	3	3	N2c	0	–	54/70 Gy	cDDP	Oro-/ hypopharynx

m male, *f* female, *5-FU* 5-fluorouracil, *cDDP* cisplatin, *R* resection status

Table 2 Definitions of boundaries of structures within the auditory system

Structure	Anatomical boundaries
Auditory nerve	Lateral: Cochlea Medial: Bony boundary of the middle cranial fossa Other: Bony boundaries of the internal auditory meatus
Eustachian tube	Cranial: Tympanic opening Caudal: Pterygoid hamulus Lateral: Ostmann’s pad of fat Medial: Pharyngeal opening Length: 34–38 mm [44] Diameter: 3–4 mm
Middle ear	Cranial: Paries tegmentalis. Aditus to mastoid antrum Caudal: Paries jugularis. Opening of the Eustachian tube Medial: Paries labyrinthicus. Promontorium Lateral: Paries membranaceus. Half the length of the bony part of the external auditory meatus Anterior: Paries caroticus. Opening of the Eustachian tube/anterior bony wall of the external auditory meatus Posterior: Paries mastoideus. Mastoid air cells/posterior wall of the external auditory meatus
Cochlea	Cochlea (f): Fluid signal in the bony labyrinth (cochlea) Cochlea (PRV): Cochlea (f) plus 3 mm margin in every direction
Vestibular apparatus	Bony labyrinth containing the fluid signals of the semicircular canals and the vestibulum

PRV planning risk volume

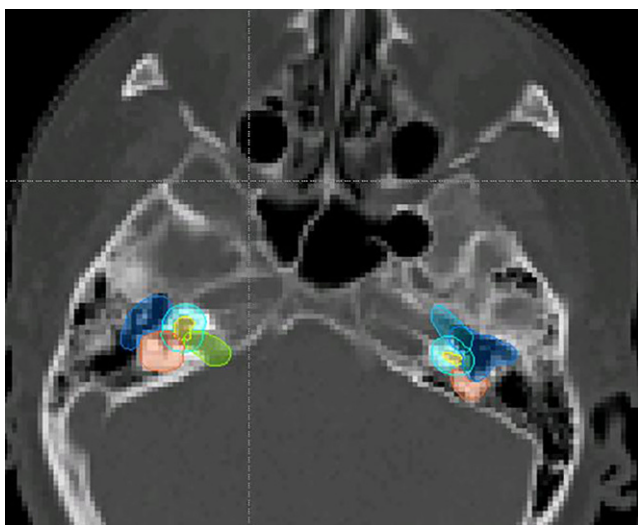


Fig. 1 Delineation of different auditory organs at risk: *yellow* cochlea (f), *light blue* cochlea (PRV), *blue* middle ear, *orange* vestibular organ, *green* auditory nerve

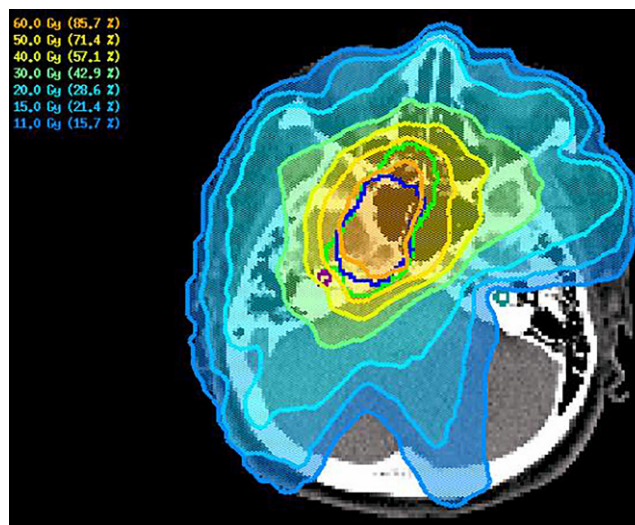


Fig. 2 Axial planning CT scan of a patient with oro-/epipharyngeal carcinoma receiving definitive radiochemotherapy with unilateral cochlea sparing; *dark blue* contour: adjuvant target volume (60Gy), *green* contour: elective target volume (54Gy)

the structures, see Table 2 and Fig. 1). Together with an otorhinolaryngologist specializing in otology, we reviewed several different contouring and anatomy atlases to develop our anatomical definition of the different structures [7, 13, 28, 33, 35]. For the cochlea, we calculated the dose for two different contours: first, for the fluid signal in the temporal bone only—“cochlea (f)” —and second, for the fluid signal with a 3 mm margin in every direction as a PRV approach—“cochlea (PRV).” The delineation of the initial target volumes and other OAR was not changed. All newly defined structures were delineated by two radiation oncologists together with the otorhinolaryngologist. We aimed to spare the cochlea on the side of the neck with the lower risk for subclinical disease (i.e., contralateral to the primary tumor and/or with less or more distant macroscopic lymph nodes). This was done by recalculating the plan with the identical constraints for target volumes and OAR used in the initial plan, except for the dose to the spared cochlea which was set below 10Gy MCD. The resulting plan was optimized until clinically applicable and the differences in the resulting equivalent uniform dose (EUD), the dose to 98% (D98), 2% (D2), and 50% of the target volume (D50), and the conformity index (CI) were recorded. An example is depicted in Fig. 2.

Results

The delineation of organs at risk (OAR) for the inner ear, middle ear, and Eustachian tubes by two radiation oncologists was very consistent, with median differences $\leq 0.1 \text{ cm}^3$, except for the tubes with a median difference of 0.7 cm^3 . In all patients, the cochlea could be spared as intended with an MCD of 6.8Gy (cochlea (f)) and 7.8Gy (cochlea (PRV)) for the adjuvant radiochemotherapy patient cohort. For the adjuvant patient cohort, the non-spared side received a mean MCD of 18.7Gy (cochlea (f)) and 18.5Gy (cochlea (PRV)). For the definitive radiochemotherapy cohort, a mean MCD of 7.6Gy (cochlea (f)) and 8.4Gy (cochlea (PRV)) was achieved while the contralateral side received 30.3Gy (cochlea (f)) and 29.8Gy (cochlea (PRV)), respectively (Table 3). Table 4 outlines the difference in MCD of the spared cochlea between the initial and the recalculated plan.

The absolute difference in EUD between the original and the recalculated plan was 0.15Gy (range $-1.2/0.6 \text{ Gy}$) for the adjuvant planning target volume and 0.05Gy (range $-0.5/0.8 \text{ Gy}$) for the boost volume (Table 5). All plans (initial and recalculated) were in accordance with the International Commission on Radiation Units (ICRU 83) report [9].

Table 3 Comparison of mean cochlear dose between spared and non-spared side in both study groups

	Adjuvant cohort		Definitive cohort	
	Spared side	Non-spared side	Spared side	Non-spared side
Cochlea (fluid)	6.8 (3.1–8.9)	18.7 (3.7–32.5)	7.6 (4–9.7)	30.3 (8.9–45.5)
Cochlea (PRV)	7.8 (3.1–10.7)	18.5 (3.7–32.4)	8.4 (4.3–11.6)	29.8 (8.8–46.2)

PRV planning risk volume, median values (range)

Table 4 Comparison of mean cochlear dose of the spared cochlea between the initial and recalculated plans

Therapy	Cochlea spared side initial	Cochlea spared side new	<i>p</i> -value
Adjuvant RCT	11.2Gy	6.4Gy	0.05
Definitive RCT	14Gy	7.4Gy	0.01

RCT radiochemotherapy, mean values, t-test

Table 5 Equivalent uniform doses in original and recalculated plans

Therapy	EUD adjuvant PTV (%)	EUD boost PTV (%)
Adjuvant RCT new plan	98 (97–100)	99 (96–100)
Adjuvant RCT initial plan	98 (97–100)	99 (97–100)
Definitive RCT new plan	98 (97–101)	100 (98–101)
Definitive RCT initial plan	98 (97–99)	100 (99–101)

RCT radiochemotherapy, PTV planning target volume, EUD equivalent uniform dose

Discussion

For advanced tumors of the head and neck region, radiochemotherapy as a definitive therapy or adjuvant to surgery is an essential part of treatment. A better understanding of the biology of the disease together with more sophisticated radiation techniques such as IMRT and the combination with systemic treatment have led to an improvement in overall survival rates [6, 31]. As the long-term survivor rates are rising, long-term toxicities are becoming more important. Unfortunately, the combination of irradiation with platinum-based chemotherapy (e.g., cisplatin) leads to higher acute and potentially long-term toxicity in normal tissues [6, 31]. However, with IMRT, it is possible to reduce the radiation dose to vulnerable organs at risk such as the parotid glands, in order to avoid long-term toxicities without compromising tumor control as has already been shown for quality of life-impairing xerostomia [10, 14, 40].

An organ known to be particularly vulnerable to cisplatin is the inner ear, particularly the outer hair cells [19, 20]. Therefore, in recent years there has been growing interest in defining a maximum radiation dose that can be safely applied to the inner ear and retrocochlear structures, particularly in combination with cisplatin. For radiation only, a dose around (35–) 45 Gy is believed to be safe to prescribe to the inner ear structures in adult patients [3]. However, there is evidence that doses lower than 45 Gy MCD can cause clinically relevant ototoxicity, especially in patients who receive a combination of radiotherapy and platinum-based chemotherapy. In this regard, Theunissen et al. found 90.7% of patients receiving combined radiochemotherapy with a median cochlear dose of 13.6 Gy to experience hearing loss according to American Speech–Language–Hearing Association (ASHA) criteria [43]. This appears to be a very high rate of hearing deterioration; however, the patients received a high-dose cisplatin regimen ($3 \times 100 \text{ mg/m}^2$) and the ASHA criteria are not as sophisticated as the Common

Terminology Criteria for Adverse Events (CTCAEv4) scoring system for ototoxicity.

To define a clear dose–effect relationship between a distinct radiation dose combined with cisplatin and the resulting ototoxicity is challenging, due to varying fractionation schemes and total doses of radiotherapy, different cisplatin regimes, heterogeneous patient collectives, different timepoints of measuring hearing levels, and diverse grading scales for the evaluation of ototoxicity [36, 37]. In a prospective study by Hitchcock et al., the relative effects of radiation and cisplatin dose on the posttherapeutic hearing levels of 62 patients were evaluated. Based on the clinical data, a mathematical model was developed to estimate the probability of clinically relevant damage to the cochlea. Following their model, in combination with weekly low dose cisplatin (40 mg/m^2), an MCD of 10 Gy or below is predicted to be well tolerated by the inner ear structures. Another essential result was the need to put a dose constraint on the cochlea. When using an inverse radiation planning approach, structures without a dose constraint may receive even higher total radiation doses than the target region, as was the case for the cochlea. Their conclusion is firstly, to put a dose constraint on the cochlea to avoid overdosing and secondly, to try to reach an MCD of 10 Gy in combination with cisplatin as long as tumor control is not compromised [15]. This might be lower than other suggested thresholds, but as an MCD of 10 Gy or below without compromising plan quality is achievable, the dose to the cochlea should be kept as low as possible, particularly with a combined radiochemotherapy approach.

The aim of our planning study was to investigate whether this MCD constraint of 10 Gy is achievable in a clinical setting with target volumes that were not designed for cochlear sparing in locoregionally advanced oro- to hypopharyngeal tumor patients. A premise for this approach was to realize a clinically applicable plan (i.e., to avoid underdosage in the target volume and overdosage in other organs at risk). Therefore, we did not include epipharyngeal tumors, since

Table 6 Differences in dose–volume parameters between initial and recalculated plans

Therapy	Adjuvant PTV					Boost PTV				
	EUD (%)	D98	D2	D50	CI	EUD	D98	D2	D50	CI
Adjuvant RCT	0	0.2 Gy (0.44)	0.2 Gy (0.16)	0.3 Gy (1.26)	1 (0.08)	0%	0.3 Gy (0.45)	0.25 Gy (0.28)	0.1 Gy (0.2)	1 (0.16)
Definitive RCT	0	0.3 Gy (0.56)	0 Gy (0.15)	0 Gy (1.08)	0.96 (0.14)	0%	0.25 Gy (0.49)	0 Gy (0.14)	0.1 Gy (0.16)	1 (0.22)

PTV planning target volume, RCT radiochemotherapy, CI conformality index, EUD equivalent uniform dose, Dx dose received by x% of the target volume, (standard deviation)

Table 7 Differences in dose–volume parameters of organs at risk between initial and recalculated plans

Therapy	Right parotid gland			Left parotid gland			Spinal cord			Brainstem		
	D98	D2	Mean	D98	D2	Mean	D98	D2	Mean	D98	D2	Mean
Adjuvant RCT	0.2 Gy (2.68)	0.3 Gy (0.35)	0.1 Gy (1.48)	0 Gy (4.96)	0.05 Gy (1.0)	0.7 Gy (3.01)	0.1 Gy (0.07)	0.35 Gy (0.71)	0.15 Gy (0.4)	0.1 Gy (0.06)	1.45 Gy (1.98)	0.05 Gy (0.62)
Definitive RCT	0.5 Gy (3.71)	0.25 Gy (0.5)	0.15 Gy (1.28)	1.3 Gy (17.8)	0.2 Gy (18.2)	0.8 Gy (1.79)	0 Gy (0.08)	0.05 Gy (1.23)	0 Gy (0.65)	0 Gy (0.14)	0.4 Gy (1.01)	0.1 Gy (0.68)

RCT radiochemotherapy, Dx dose received by x% of the organ at risk volume, (standard deviation)

in most of these patients, there is no option to spare the cochlea to an MCD of 10 Gy or below as the GTV or at least the high-risk PTV is directly adjacent to the middle and inner ear structures. Furthermore, the incidence of these tumors is far lower, rendering a prospective investigation with adequate numbers challenging.

We achieved an MCD of 10 Gy or less in all recalculated plans for this locally advanced head and neck cancer patient collective. All plans were in accordance with the ICRU 83 report. The resulting mean EUDs of the PTC were identical between the initial and the recalculated plans, indicating that the dose coverage of the PTVs was not compromised. Regarding target volume coverage in terms of D2, D98, D50, and conformality index, there were no relevant differences between the plans (Table 6). Furthermore, the median difference in dose to the investigated OAR is almost unchanged (Table 7).

We could demonstrate that it is feasible to attain a consistent delineation of the cochlea in a 3 mm planning CT scan. Nevertheless, for small structures like the cochlea, a slice thickness of 1 or 2 mm would be more suitable. However, the evaluation of the MCD for the cochlea and the cochlea PRV showed only small differences, indicating that OAR variations of a few millimeters do not change the results significantly.

Potential clinical benefits of unilateral sparing of the cochlea for the patient may be the following: Firstly, if serviceable hearing on at least one side can be preserved, this has an enormous impact on the patient’s social participation, as it facilitates communication, e.g., on the telephone. Secondly, sparing the vestibular organ as well as the acoustic nerve can be crucial to avoid posttherapeutic vertigo and postural problems [5, 12], as well as to permit

hearing rehabilitation by cochlea implantation, if necessary [1, 21–23]. Thirdly, besides the vestibulocochlear organ, the temporal bone itself will be spared excessive radiation doses. Therefore, the risk for temporal osteoradionecrosis, ageusia caused by lesions of the chorda tympani, and temporomandibular joint dysfunction may be reduced [18, 34].

There have already been attempts to perform cochlea-sparing radiotherapy in head and neck cancer patients. In a prospective study by Zuur et al. including 101 patients treated with radiation therapy only, a dose constraint was put on the cochlea according to the “as low as reasonably achievable” (ALARA) principle. The median dose to the cochlea was 17.8 Gy and the short-term hearing deterioration was negligible [38, 42]. In long-term follow-up of the remaining 36 patients, hearing loss due to radiation therapy remained subclinical [38]. Use of the ALARA principle for the cochlea represents a valuable tool for reducing radiation-associated ototoxicity, but unfortunately, no conclusion for the combined therapy can be drawn.

A study by Nguyen et al. demonstrated that tomotherapy can reduce MCD in comparison to IMRT in head and neck cancer patients [26, 27]. However, tomotherapy is not the standard radiation technique for head and neck tumors, and it is not widely available. Nevertheless, for a certain patient collective (e.g., locally advanced nasopharyngeal tumors), it might be beneficial for cochlea sparing due to its steeper dose gradient [11, 26].

Conclusion

The primary goal in cancer patients is to achieve long-lasting tumor control. With an increasing number of long-term

survivors, quality of life is essential. Posttherapeutic xerostomia, trismus, fibrosis, and dysarthria are common in head and neck cancer patients. Additional hearing impairment potentiates the difficulties in communication. We believe that the impact of hearing loss on the socioeconomic status of these patients is still underestimated. Defining the cochlea as an avoidance structure is not routinely recommended in treatment protocols and contouring atlases, possibly leading to overdosage in the cochlea [15]. Our study demonstrates that a unilateral MCD of 10Gy appears feasible without compromising target coverage in a locally advanced patient cohort. The clinical effects of this strategy should be prospectively investigated.

Conflict of interest L.H. Braun, K. Braun, B. Frey, S.M. Wolpert, H. Löwenheim, D. Zips, and S. Welz declare that they have no competing interests.

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