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Hearing Loss After Cisplatin-based Chemoradiotherapy for Locally Advanced Head and Neck Cancer: A Prospective Single-institution Study

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Abstract. *Background/Aim: A single-institution prospective study was conducted to evaluate hearing loss rate after intensity modulated radiotherapy with concomitant cisplatin-based chemotherapy (CRT) for locally advanced head and neck cancer and identify cochlear dosimetric parameters associated with hearing loss risk. Patients and Methods: Hearing assessment, patients' characteristics, tumor-related variables, and cochlear quantitative dosimetric factors for adults with locally advanced head and neck cancer treated with CRT were prospectively collected. Each patient repeated audiometry at baseline (pre-CRT), 1 month after CRT, and then every 3 to 6 months. For each cochlea minimum dose (D_{min}), mean dose (D_{mean}), and maximum dose (D_{max}) were extracted from treatment plans. Logistic analysis was used for multivariate modeling. The relation between cochlear dosimetric factors and significant hearing loss was also analyzed with receiver operating characteristic (ROC) curves. Results: Between January 2016 and December 2018, 35 patients (70 cochleae) were included. Most patients (n=29; 82.9%) had primary cancer in a low-risk region (oral cavity, oropharynx, larynx). All patients completed the programmed CRT. During follow-up, significant hearing loss was recorded in 13 cases (37.1%). The ROC areas for significant hearing loss in relation to D_{min}, D_{mean}, and D_{max} were 0.70, 0.66, and 0.66, respectively. A dose-dependent relationship was noted between cochlear D_{min} and significant hearing loss. Conclusion: D_{min} <14.4 Gy is associated with reduced rates of significant hearing loss after concomitant cisplatin-based CRT in patients with locally advanced head and neck cancer.*

Definitive or adjuvant radiotherapy (RT) with concomitant cisplatin-based chemotherapy (CRT) is often recommended in the treatment of patients with locally advanced head and neck cancer (1, 2). Despite advances in RT technique, a significant number of patients will experience treatment-related toxicities that negatively affect their quality of life (QoL).

Over the years, dysfunction of hearing apparatus has become an important area of investigation for radiation oncologists, conscious that the RT damage to the cochlea is further aggravated by concurrent cisplatin systemic therapy (3). While it is well known that several factors – including patient's age and baseline hearing level, cumulative cisplatin dose, post-RT otitis media onset – affect the risk of hearing loss, it remains undefined which of the cochlear RT dose parameters – minimum dose (D_{min}), mean dose (D_{mean}), maximum dose (D_{max}) – are most predictive of sensorineural hearing loss (3, 4).

Given the need to minimize the risk of severe hearing loss, we conducted a prospective study to quantify cochlear dose/hearing loss relationship aiming at a further improvement of counseling of patients with locally advanced head and neck cancer.

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Key Words: Head and neck cancer, hearing loss, cisplatin, radiotherapy, concomitant treatment, toxicity, cochlea, constraints, dose.

Patients and Methods

Population and treatment characteristics. Consecutive patients with a locally advanced head and neck cancer treated with either definitive or adjuvant CRT were registered on this prospective longitudinal study. The study was approved by the institutional review board (ref. 6452) and written informed consent was obtained from all patients before treatment. All cases were discussed in a multidisciplinary head and neck meeting before CRT initiation. Patients with severe hearing loss at diagnosis and those who received a non-curative intent approach were excluded. Preventive dental care and nutrition evaluations occurred before treatment (5). Concurrent chemotherapy consisted of three-weekly cisplatin scheme (100 mg/m^2). All patients were treated with intensity modulated technique (IMRT). Definitive CRT was delivered using a simultaneous integrate boost (SIB) at a total dose of 67.5 Gy with a 2.25 Gy daily fraction to the macroscopic disease, 60 Gy to the intermediate-risk region at 2 Gy per fraction, and 54 Gy to the low-risk region at 1.8 Gy per daily fraction. Adjuvant CRT was delivered using a sequential approach to a total dose of 50 Gy to prophylactic target volume plus 16 Gy to the tumor bed with 2 Gy conventional fractionation. Follow-up was scheduled according to the policy of the institution, and included clinical and diagnostic examinations, where appropriate, at 6-week intervals for the first year, then every 3 months for the next two years, and every 6 months thereafter (6).

Bilateral cochleae were contoured by a single radiation oncologist (DM) for dose-volume histogram analysis. For each patient, dosimetric parameters, including D_{mean}, D_{min} and D_{max} were calculated for the left cochlea and right cochlea from the treatment plan.

Hearing assessment. All patients were evaluated before CRT with baseline audiometry. As per study design, in order to describe the full impact of hearing damage, each patient repeated follow-up audiometry 1 month after treatment and then every 3 to 6 months for the first year. The hearing threshold level was assessed at each frequency and pure tone average was calculated as the average of threshold levels at 500, 1,000, 2,000, and 4,000 Hz frequencies. An increase of 10 dB at the key human speech frequencies in post-treatment bone conduction threshold was considered a clinically significant hearing loss (7-9).

Primary endpoint. The primary endpoint was to estimate a relationship between the frequency of significant hearing loss at the worst audiometric evaluation and the cochlear radiation dose in head and neck patients treated with cisplatin-based CRT.

Statistical analysis. Statistical analysis was performed using R-Studio 0.98.1091 software and SPSS v18.0 software. Standard descriptive statistics were used to evaluate the distribution of each variable. Continuous variables were reported as mean±standard deviation (SD) and categorical variables as frequencies or percentages. To define significant predictors of hearing loss rate, clinical-related variables – age at diagnosis, sex, comorbidity, smoke, alcohol, performance status (PS), primary location, clinical T classification (cT), and clinical nodal status (cN) – and dosimetric-related parameters (D_{mean}, D_{min} and D_{max}) were investigated. Primary disease located in the nasopharynx and parotid gland regions were categorized as high-risk locations for radiation-induced cochlear damage. Other primary sites were considered as low risk location. Univariate analysis was performed using the Fisher's test. The dependent variable referred to significant hearing loss evidence (no or yes). Receiver operating characteristic (ROC) curves were used to identify the reference threshold of potential dosimetric cut-off value predictors. A higher area under the ROC curve (AUC) indicates a more powerful predictor. To evaluate the relationship between significant hearing loss and radiation dose, each cochlea was analyzed independently. When plotting the data, cochleae were grouped according to the quartiles of the dose distribution and the significant hearing loss rate was calculated for each group. Variables associated with a p-value of <0.20 were included in a logistic regression analysis. All reported p-values are two-sided, and p-values lower than 0.05 were considered significant.

Results

Study group. Between January 2016 and December 2018, 35 patients (70 evaluable cochleae) were enrolled. Patient and primary tumor characteristics are listed in Table I. The group consisted of 25 men (71.4%) and 10 women (28.6%). The mean age at diagnosis was 61.2 years (range=27.0-74.0 years). Definitive treatment was prescribed to 20 patients (57.1%) and postoperative treatment to 15 patients (42.9 %). All patients (n=35, 100%) completed the programmed CRT. Overall, 35 patients (100%) received the RT prescribed total dose and 28 patients (80.0%) achieved a cumulative cisplatin dose ≥200 mg/m^2.

During the follow-up period, there were no patients who experienced post-CRT otitis media. Thirteen patients (37.1%) reported significant hearing loss. Of these 13 cases, all patients (100%) had mild hearing loss at diagnosis. Six patients (46.2%) experienced worst hearing loss 1 month after CRT, three patients (23.1%) 3 months after treatment, one patient (7.6%) 6 months after and 3 patients (23.1%) 12 months after the end of CRT. Hearing loss assessments as a function of time in these patients is depicted in Figure 1. A general prevalence of severe hearing loss (grade ≥3) was recorded 1-3 months after treatment persisting without (or with relative) improvement thereafter. Incidence of post-treatment significant hearing loss was not related to clinical variables. Details are presented in Table I.

Hearing loss and dosimetric parameters. To assess the relationship between radiation dose to the cochlea and significant hearing loss, each cochlea was analyzed independently. Of the 70 cochleae in the 35 patients, 16 cochleae (22.9%) in 13 cases were graded as having moderate/severe hearing loss during follow-up. A summary of the dosimetric parameters is shown in Table II. A D_{min} of 14.4 Gy successfully identified patients who were at risk of developing significant hearing loss (Figure 2). The AUC was 0.70 [95% confidence interval (CI)=0.54-0.83] with a sensitivity and specificity of 0.52 and 0.84, respectively. Of the 18 cochleae with D_{min} ≥14.4 Gy, significant hearing loss was detected in 55.6% of cases (n=10). Significant hearing loss risk was reduced at 11.5% (6 out of 52) in those cochleae receiving D_{min} <14.4 Gy. Whereas a D_{mean} of 20.9 Gy and a D_{max} of 19.1 Gy were observed to have a borderline significant

Table I. *Patient and primary tumor characteristics*.

Variables	No significant hearing loss (n=22)	Significant hearing loss (n=13)	Total (n=35)	*p*-Value
Age				0.512
Mean (SD)	60.4 (10.3)	62.6 (8.0)	61.2 (9.4)	
Range	27.0-74.0	46.0-73.0	27.0-74.0	
Sex				0.319
Male	17 (77.3%)	8 (61.5%)	25 (71.4%)	
Female	5 (22.7%)	5 (38.5%)	10 (28.6%)	
Comorbidity				0.414
None	7 (31.8%)	2 (15.4%)	9 (25.7%)	
Cardiac	12 (54.5%)	10 (76.9%)	22 (62.9%)	
Multiple	3 (13.6%)	1 (7.7%)	4 (11.4%)	
Smoke				0.974
Never	3 (13.6%)	2 (15.4%)	5 (14.3%)	
Former	11 (50.0%)	6 (46.2%)	17 (48.6%)	
Current	8 (36.4%)	5 (38.5%)	13 (37.1%)	
Alcohol				0.253
Never	20 (90.9%)	10 (76.9%)	30 (85.7%)	
Current	2 (9.1%)	3 (23.1%)	5 (14.3%)	
Performance status				0.263
≤1	20 (90.9%)	13 (100.0%)	33 (94.3%)	
>1	2 (9.1%)	0 (0.0%)	2 (5.7%)	
Primary location				0.706
Oral cavity	4 (18.2%)	4 (30.8%)	8 (22.9%)	
Oropharynx	12 (54.5%)	6 (46.2%)	18 (51.4%)	
Larynx	2 (9.1%)	1 (7.7%)	3 (8.6%)	
Nasopharynx	2 (9.1%)	0 (0.0%)	2 (5.7%)	
Salivary gland	2 (9.1%)	2 (15.4%)	4 (11.4%)	
High risk primary location*				0.832
No	18 (81.8%)	11 (84.6%)	29 (82.9%)	
Yes	4 (18.2%)	2 (15.4%)	6 (17.1%)	
cT (7^{th})				0.394
1	4 (18.2%)	0 (0.0%)	4 (11.4%)	
2	8 (36.4%)	6 (46.2%)	14 (40.0%)	
3	3 (13.6%)	3 (23.1%)	6 (17.1%)	
4	7 (31.8%)	4 (30.8%)	11 (31.4%)	
cN (7^{th})				0.636
0	3 (13.6%)	3 (23.1%)	6 (17.1%)	
1	1 (4.5%)	2 (15.4%)	3 (8.6%)	
2	2 (9.1%)	0 (0.0%)	2 (5.7%)	
2a	2 (9.1%)	0 (0.0%)	2 (5.7%)	
2b	4 (18.2%)	2 (15.4%)	6 (17.1%)	
2c	7 (31.8%)	5 (38.5%)	12 (34.3%)	
3	3 (13.6%)	1 (7.7%)	4 (11.4%)	
Cumulative cisplatin dose				0.162
<200 mg/m^2	6 (27.3%)	1 (7.7%)	7 (20.0%)	
≥200 mg/m^2	16 (72.7%)	12 (92.3%)	28 (80.0%)	

*High-risk primary location: nasopharynx and parotid gland region. SD: Standard deviation; cT: clinical tumor classification; cN: clinical node classification; mg/m^2: milligram per square meter.

predictor with a predictive ability of 0.66 (95%CI=0.51-0.80) and 0.66 (95%CI=0.51-0.81), respectively. Univariate analysis indicated that none of the clinical variables were determining factors for the development of hearing loss. The probability of significant hearing loss as a function of D_{min} is shown in Figure 3. For higher frequencies, a dose-dependent relationship was demonstrated.

Discussion

Our study confirmed that patients with locally advanced head and neck cancer can develop significant hearing loss after cisplatin-based CRT despite of IMRT planning technique. The cumulative incidence of significant hearing loss was 37.1%. Clinical-related variables were not found to be risk

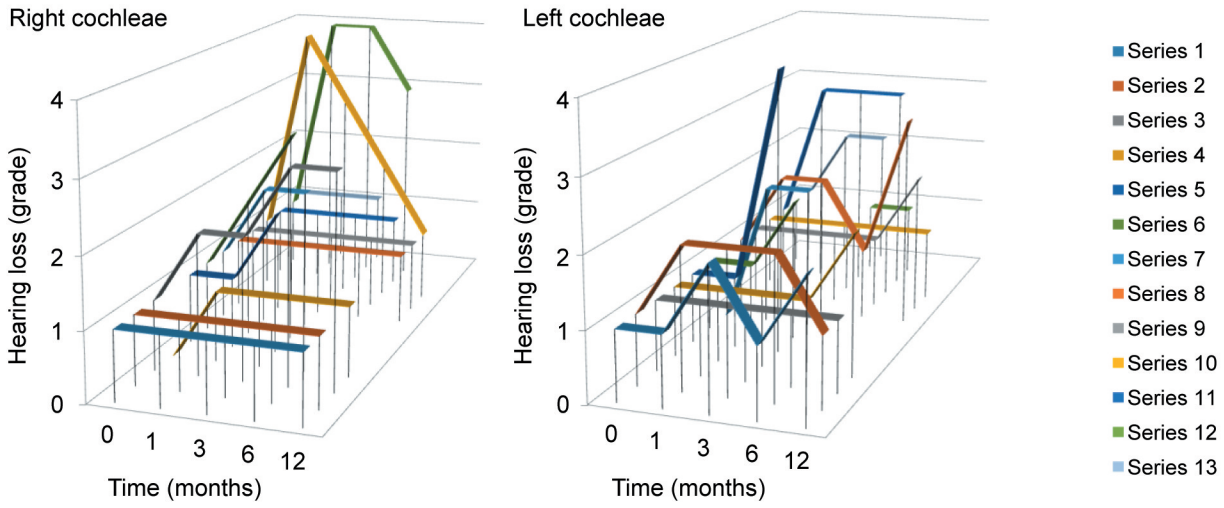

Figure 1. *Hearing loss evaluation at diagnosis (0) and 1, 3, 6, 12 months after chemoradiotherapy in patients with significant ototoxicity.*

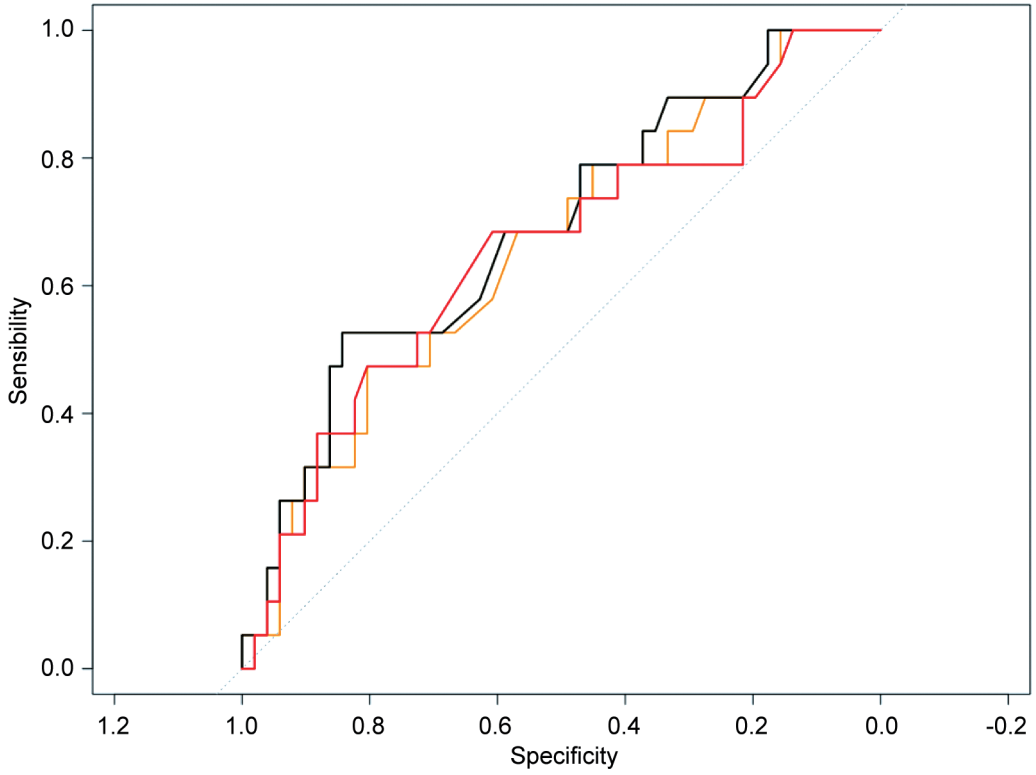

Figure 2. *Receiver operating characteristic curve of dosimetric parameters D_{min} (black), Dmean, (orange) and D_{max} (red).*

factors for hearing loss development. Audiology assessment was important throughout our analysis. Most significant hearing loss was first noted 1 to 3 months after CRT completion and the ototoxicity was persistent, demonstrating that the hearing loss risk mainly began soon after treatment and continued long after. Individual sides of enrolled patients were analyzed independently to account for differences in RT doses received. D_{min} to cochlea correlated with hearing

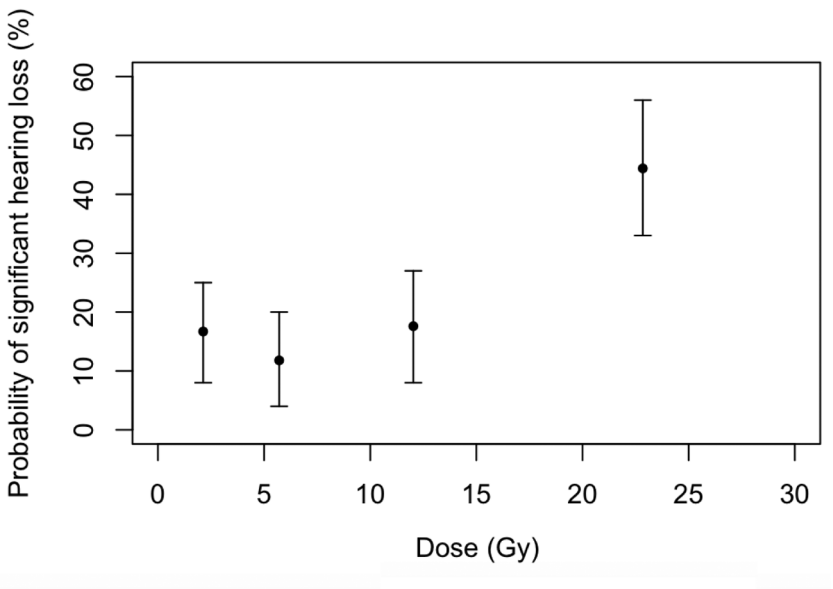

Figure 3. *Probability of significant hearing loss as a function of minimum cochlea dose.*

Table II. *Summary of dosimetric parameters (70 cochleae).*

Dosimetric parameter	No significant hearing loss (n=54)	Significant hearing loss (n=16)	Total (n=70)	*p*-Value
D_{mean}				0.142
Mean (SD)	13.2 (11.1)	18.1 (13.1)	14.3 (11.6)	
Range	1.5-43.7	1.4-45.9	1.4-45.9	
D_{min}				0.042
Mean (SD)	9.7 (8.6)	14.1 (10.5)	10.7 (9.2)	
Range	1.4-39.7	1.3-41.0	1.3-41.0	
D_{max}				0.158
Mean (SD)	16.9 (13.9)	22.7 (16.0)	18.2 (14.5)	
Range	1.7-52.4	1.6-50.0	1.6-52.4	

SD: Standard deviation.

loss. The prevalence of hearing loss was significantly lower in patients who received D_{min} <14.4 Gy (11.5% *versus* 55.6%). We considered 11.5% an acceptable risk of toxicity and therefore, we suggested 14.4 Gy as the maximal D_{min} to the cochlea. Because of the cochlea's small anatomic structure, our suggestion indicates the need for accurate contouring and setup as routine practice to ensure the calculation of the predictive cochlear dose. For sure, a dose-volume analysis is impractical. In scientific literature, some data are available on cochlear dose constraints (Table III) (10-18). A variable range of radiation doses caused cochlear damage. Most studies only investigated the correlation of cochlear D_{mean} to persistent hearing loss, whereas few explored other radiation dosimetric parameters. Actually, cochlea might be a serially organized organ and thus the D_{mean} might not be the best predicting factor for RT-related hearing loss (11). We used D_{max}, D_{mean}, and D_{min} to the cochlea as dosimetric parameters and found that D_{min} correlated better than the other doses. Our findings suggested that limiting the cochlear D_{min} to <14.4 Gy and potentially restricting D_{max} to 19 Gy resulted in more patients with preserved hearing. Whether these dosimetric parameters will be applicable in clinical practice is questionable. Actually, the vast majority of our patients (82.9%) had primary cancer in a low-risk region – in which the cochleae was further away from the radiation field, with a much lower cochlear radiation dose than that in a high-risk region – facilitating a potential cochlear-sparing RT in this setting. The combined effects of irradiation and ototoxic chemotherapy should not be underestimated and therefore, when patients receive concurrent cisplatin-based CRT for low-risk region tumors, cochlear dose should be as low as reasonably achievable to

Table III. *Cochlea threshold dose*.

Author	Patient (n)	Primary tumor	Treatment	Cochlea dosimetric parameters
Hitchcock *et al*. 2009 (10)	62	HNC	(C)RT	Dmedian < 40 Gy
Wang *et al*. 2015 (11)	51	Nasopharynx	CRT	D_{max} ≥ 39.8 Gy
Zhu *et al*. 2019 (12)	70	Nasopharynx	RT	D_{min} 25.76 (LF), 29.94 (HF); D_{max} 35.51 (LF), 34.75 (HF); D_{mean} 29.45 (LF), 34.02 (HF)
Pan *et al*. 2009 (13)	35	HNC	RT	D_{max} > 45 Gy
Chen *et al*. 2006 (14)	22	Nasopharynx	CRT	D_{mean} > 48 Gy
Van der Putten *et al*. 2006 (15)	52	Parotid gland	RT	D_{mean} > 50 Gy
Yip *et al*. 2021 (16)	81	Nasopharynx	CRT	D_{min} > 44 Gy, D_{mean} > 52 Gy, D50 > 54Gy, V45 > 90%, V50 > 86%, V55 > 4%, V60 > 10%
Hermann *et al*. 2006 (17)	18	HNC	RT	D_{mean} 20 Gy
Honoré *et al*. 2002 (18)	11	Nasopharynx	CRT	D_{mean} 15 Gy

HNC: Head and neck cancer; (C)RT: (chemo)radiotherapy; D: dose; LF: low frequencies; HF: high frequencies; V: volume.

decrease the incidence of hearing loss. The effect of concomitant cisplatin-based chemotherapy on hearing function has been proven, but the safety profile of CRT remains a challenging question, as it is difficult to investigate. Indeed, the risk of hearing loss is directly linked to patients' characteristics, mainly individual baseline hearing thresholds and age (9). Accordingly, all our patients who developed hearing loss had mild hearing loss at diagnosis, though assumption of linearity was not statistically confirmed. Adjustment for these individual risk factors should be considered in these patients due to their substantially increased risk of hearing loss even at the lowest RT doses. In the scientific literature, other studies have documented hearing loss after radiation to the cochlea. It should be noted that different definitions of hearing loss were used that made difficult a direct and robust comparison between studies (9). Our study did not allow a detailed analysis of the audiometric frequencies, since we did not define the minimum number of audiometry used to define the grade of toxicity. We defined clinically significant hearing loss according to quantitative analyses of normal tissue effects in the clinic (QUANTEC) guideline (9). Nevertheless, our results were consistent with those studies showing that RT-induced hearing loss was more often seen at higher frequencies (10).

This study has several limitations. First, the study population was heterogeneous in terms of primary tumor location. However, all patients were treated with a curative intent for locally advanced disease and received the same RT and cisplatin-based regimen. Second, one can argue if the 7th TNM edition is still adequate to stage head and neck cancer patients at diagnosis. However, considering that the CRT prognostic value was not addressed at all, we believe that the stage at diagnosis has no impact on the primary end-point of the study. Third, the study is limited to one institution setting and needs to be externally validated. Lastly, the relative limited number of patients did not allow for a meaningful multivariate analysis. The interaction between dose and clinically-related variables needs to be further investigated before reaching any conclusion.

Despite these limitations, we hope that this study can make a valuable contribution to the literature. We support the indication of a dose constraint of 14.4 Gy to the cochlea for head and neck cancer patients receiving cisplatin-based CRT without compromising target coverage.

Conclusion

D_{min} <14.4 Gy to the cochlea was the most relevant dosimetric parameter to assess the probability of developing hearing loss after concomitant cisplatin-based CRT in patients with locally advanced head and neck cancer.

Conflicts of Interest

The Authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contributions

Conceptualization: DM, AM. Data acquisition: DM, PDU, VM, LZ. Data analysis, methodology: FDF, CM. Writing – original draft: FDF. Writing – review: DM, MdV, MR, VT. Final approval: all Authors.

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