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Short Communication

Effects of radiotherapy for tumors of the larynx and hypopharynx in hearing levels

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ABSTRACT

The head and neck oncological patients are susceptible, either because of tumor location or the treatments performed, to changes of their ear structures. Due to close proximity of radiation field to the ear, radiotherapy induces short and long-term toxicities to the external, middle and internal ear. The aim of this study was to evaluate the impact of radiotherapy on the inner ear. We conducted a cross-sectional retrospective study of patients with cancer of the larynx and hypopharynx undergoing radiotherapy alone or adjuvant to surgery. The follow-up period was 1 year. Relevant clinical and audiological variables were analyzed. We included 15 patients, mostly males, with a median age of 66 years. Average hearing threshold (AHT) deterioration was found in 13 ears, with a median of 8.1dB. Mean bone conduction threshold at 4000 Hz, air conduction threshold at 8000 Hz at 12 months and the median of the final air conduction threshold at 10,000 Hz was significantly higher than the pre-treatment. A correlation was observed between final AHT and dosage of radiation per fraction. Thus, for each increase of 1 Gy per fraction there was an increase of 22.13 dB in the final AHT. About half of the patients had deterioration of the final AHT, proving, on the one hand, the sensorineural hearing loss associated with radiotherapy, while emphasizing the need to perform long-term follow-up protocols for early auditory rehabilitation of these patients.

Keywords: Radiotherapy, Larynx, Hypopharynx, Sensorineural hearing loss, Hearing thresholds, High frequency audiometry

INTRODUCTION

Approximately 80% of patients with head and neck cancer are treated with radiotherapy (RT) at least once during the course of their disease.[1] This therapy plays a fundamental role in the management of these patients by restricting the reproductive potential of tumor cells, inducing their death by apoptosis, necrosis, among other cellular phenomena.[1] However, these effects do not apply only to tumor cells, for harmful effects of RT are observed in healthy tissue adjacent to the tumor. Nevertheless, strategies are employed to minimize damage to vital structures such as the brainstem, optic chiasm, eyes or pituitary gland.[2] Well established chronic (duration >3 months) side effects of RT include dysphagia, xerostomia, osteoradionecrosis of the jaw and trismus.[1]

The anatomical proximity of the various head and neck structures to the ear often includes it in the field of irradiation.[3] Indeed, RT may affect any component of the auditory pathway.[3] In the external ear, it can induce acute and late reactions to the skin of the pinna, external auditory canal and periauricular region, including erythema, desquamation, ulceration, atrophy, stenosis, otitis externa and necrosis.[3] In the middle ear, it is most commonly associated with transient otitis media with effusion due to eustachian tube dysfunction, but it also can induce permanent changes, thickening, atrophy or perforation of

the tympanic membrane and ossicular chain atrophy.[3] Morbidities in the inner ear include tinnitus, labyrinthitis, canal paresis, vertigo and balance issues, and sensorineural hearing loss (SNHL).[4] Although to a lesser extent compared to cochlear structures, the retrocochlear pathway can also be compromised, as studies have shown auditory brainstem dysfunction, with prolonged latencies for waves I, III and V in auditory brainstem responses (ABR).[5]

Radiation-induced sensorineural hearing loss is thought to be caused by vascular insufficiency, with progressive degeneration and atrophy of inner ear sensory structures, including damage to the organ of corti (inner and outer hair cells), stria vascularis, spiral ganglion and cochlear nerve, fibrosis, ossification of inner ear fluids.[3] SNHL can be sudden or progressive, transient or permanent, and acute or delayed.[3] The latter form develops 6 to 24 months after irradiation, and is frequently chronic, irreversible and progressive, since it may progress to cophosis in a few weeks or months.[3] Thus, radiation dose to the inner ear should be minimal, particularly in patients receiving cisplatin.[4] In fact, some studies suggest chemotherapy may increase the likelihood of developing sensorineural hearing loss, with a dose and sequence dependent effect, since patients developed increased toxicity when chemotherapy was given after RT compared to pre-RT administration.[4] Some even suggest replacing cisplatin with a less potent ototoxic chemotherapy agent like carboplatin.[4]

All patients that undergo radiotherapy for head and neck tumors should have a baseline otologic examination, that includes microscopic otoscopy and pure-tone audiometry, tympanometry and stapedial reflexes, and the subsequent follow-up should be long-term, for at least three year after treatment, and include serial audiometric evaluation, complemented with otoacoustic emissions, ABR or, ideally, imaging, with computed tomography or magnetic resonance imaging, which are important for evaluation of both patency and fibrosis of inner ear fluid and spaces.[3]

Radiotherapy-related ototoxicity is well established in cases where radiation to the ear is unavoidable, such as in tumors of the nasopharynx, parotid, or skull base; however, the literature is scarce regarding its effects in other locations of the head and neck, such as in tumors of the larynx and hypopharynx.

The objective of the present study was to evaluate the impact of radiotherapy applied to these tumors on the inner ear.

METHODS

This was a cross-sectional retrospective cohort study to assess patients diagnosed with carcinoma of the larynx and hypopharynx who underwent primary or complementary treatment with radiotherapy at the Otorhinolaryngology Department of Instituto Português de Oncologia de Coimbra – Francisco Gentil from January 2021 to December 2022. The maximum follow-up period was 1 year for each patient. Patients undergoing primary or adjuvant chemotherapy were excluded from the sample.

By consulting the clinical files, the following clinical variables were analyzed and grouped: demographics - age and gender; co-morbidities and ototoxic medication, staging, treatment; dose, fractioning, duration and location of irradiation; tonal audiogram which included the frequencies of 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz and 8000 Hz; and high frequency tonal audiogram which included the frequencies of 10 000 Hz, 12.5 000 Hz, 16 000 Hz and 20 000 Hz.

Tonal audiometry was performed by the same audiologist, before treatment, and often after the end of treatment - immediately after, at 6 or 12 months after treatment. In order to select only the effect of radiotherapy on the inner ear, the bone conduction thresholds in the frequencies of 250 to 4000 Hz and the air conduction thresholds in the frequencies of 8000 to 20 000 Hz were evaluated. The Average hearing threshold (AHT) was calculated as the average of the frequencies 500, 1000, and 2000 Hz, and was assessed individually for the ear ipsilateral and contralateral to the tumor. Hypoacusis was assumed when the average hearing threshold was greater than 20 dB. AHT deterioration was considered significant if greater than 10 dB.

Data analysis was performed with statistical package for the social sciences (SPSS)® software, version 27.0. Discrete variables are presented as frequencies and percentages and continuous variables are summarized with mean and standard deviation (SD) with normal distribution or medians and interquartile range (IQR) in variables with non-normal distribution. Chi-square test or Fisher test was used for comparison between groups for categorical variables, and student's t-test and linear regression test for continuous variables. Simple linear regressions were performed to assess the existence of predictors of final pure-tone average thresholds. Statistical significance was assumed for p values <0.05.

RESULTS

Fifteen patients were included, most of them male, aged 60-84 years (median 66 years, IQR of 20), and the primary tumor was stage IV in 7 patients. Single modality radiotherapy was performed in 7 patients and adjuvant surgery in the remaining 8 patients. The median total dose of irradiation was 60 Gray (Gy) (IQR=16), during 6 weeks (IQR=2.5) of treatment divided into 30 fractions (IQR=13), with a median of 2.1 Gy (IQR=1) per fraction performed once a day. Irradiation was performed in the laryngeal and neck region (mostly bilateral) in 10 patients, and in 5 patients it was only applied in the larynx/hypopharynx region. Of the main comorbidities of the patients evaluated, arterial hypertension (53.3%) stands out, 25% of these chronically medicated with ansa

diuretics, followed by dyslipidemia and chronic obstructive pulmonary disease in the same percentage of patients (20%). About 20 ears presented with initial AHT deterioration, mostly mild (75%) (Table 1).

Table 1: Patients' characteristics.

Variable	Frequency	Percentage
Gender		
Male	14	93.3
Female	1	6.7
Comorbidities		
≤1	7	46.7
≥2	8	53.3
Overall stage		
I	1	6.7
II	2	13.3
III	5	33.3
IV	7	46.7
Initial hearing loss	20	66.7
Degree of hearing loss		
Mild (21-40 dB)	15	75
Moderate (41-70 dB)	5	25
Treatment		
Radiotherapy	8	53.3
Radiotherapy + surgery	7	46.7
Radiation field		
Larynx/hypopharynx	5	33.3
Larynx/hypopharynx + neck	10	66.7

The mean AHT of each ear was 24.35 dB (SD=11.17) pre-treatment, 30.11 dB (SD=13.08) post-treatment, 34.33 dB (SD=13.36) at 6 months, and 32.14 dB (14.43) at 12 months. For each ear, the mean AHT of the ear ipsilateral to the tumor at the same timings was 28.06 dB (SD=12.31), 30 dB (SD=15.09), 35 dB (SD=10.54) and 30.47 dB (SD=15.69), respectively. In the contralateral ear was 23.61 dB (SD=12.97), 26.94 dB (SD=12.88), 33.67 dB (SD=17.01) and 33.80 dB (SD=14.10), respectively (Figure 1).

In order to assess the evolution of thresholds over time, we carried out a paired sample of mean hearing thresholds, and we noticed that the mean of post-treatment average hearing threshold was significantly higher than the pre-treatment one (p=0.045).

The mean bone conduction threshold at 4000 Hz frequency were, respectively, 47.12 dB (SD=17.62) pre-treatment, 55.71 dB (SD=16.16) at the end of treatment, 54 dB (SD=16.63) at 6 months, and 58.57 dB (SD=15.86) at 12 months. The mean air conduction threshold at 8000 Hz in both ears at the same observation times was 68.65 dB (SD=21.71), 71.43 dB (SD=22.49), 82 dB (SD=23.71) and 78.21 dB (SD=19.07), respectively. The mean bone conduction threshold at 4000 Hz at 12 months, and air conduction threshold at 8000 Hz at 12 months were significantly higher than their pre-treatment ones (p=0.031 and p=0.057, respectively) (Figure 2).

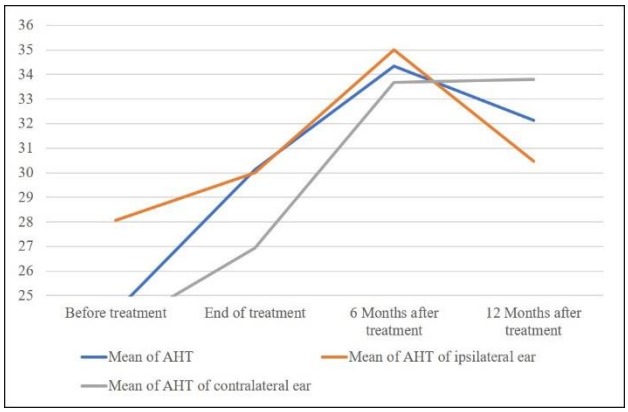

Figure 1: Evolution of the average hearing threshold (dB) before treatment, after treatment, at 6 and 12 months after treatment.

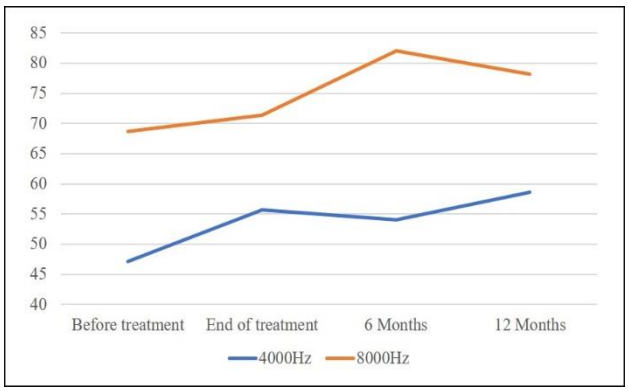

Figure 2: Evolution of the average bone conduction threshold at 4000 Hz and air conduction threshold at 8000 Hz frequencies before treatment, after treatment, at 6 and 12 months after treatment.

As to high frequencies, we noticed threshold changes in the frequencies of 10,000 Hz and 12,500 Hz. The median of the final air conduction threshold at 10,000Hz frequency ($\tilde{x}$=70 dB; IQR=36.25) was significantly superior than the initial one ($\tilde{x}$=82.5 dB; IQR=23.75) (p=0.030). The same did not occur for the frequency of 12,500 Hz, since the initial and final median of air conduction threshold was 90 dB (IQR=36.25) and 88.75 dB (IQR=16.88), respectively (p=0.251).

We compared the mean hearing thresholds relative to the initial and last available audiometric evaluation. A deterioration in the final AHT was observed in 13 ears (43.3%), with a median difference of 8.7dB (IQR=6.84), occurring bilaterally in 4 patients and unilaterally in 5 patients. This deterioration was significant (greater than 10 dB) in only 38.5% of the cases. The final degree of hearing loss remained similar to the previous one in most cases, and only in 3 of the 20 ears with initial hearing loss there was progression from a mild to moderate degree.

Deterioration of the bone conduction threshold at 4000Hz was seen in 15 ears (50%), bilateral in 5 patients, with a median value of 10 dB (IQR=10), and of the air conduction threshold at 8000 Hz in 14 ears (46.7%), bilateral in 5 patients, with a median value of 17.5 dB (IQR=22.5). This deterioration was greater than 10 dB in 10 and 9 ears, respectively (Figure 3).

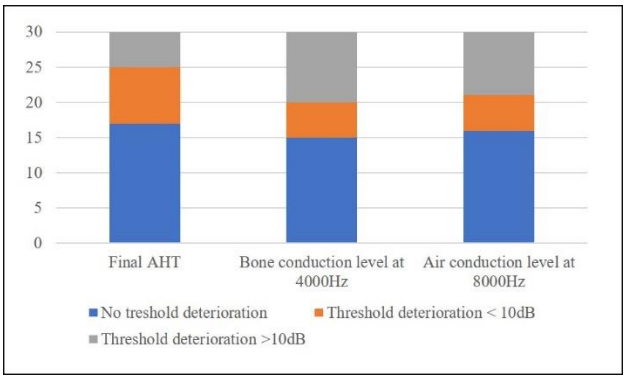

Figure 3: Distribution of final thresholds deterioration - AHT, bone conduction at 4000 Hz and airway at 8000 Hz (dB) - by ear.

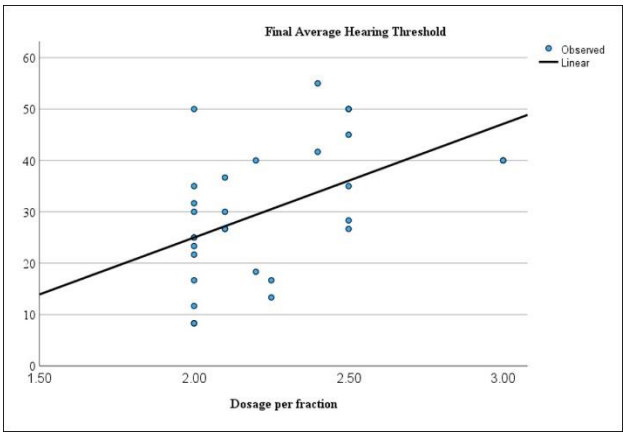

Figure 4: Simple linear regression between dosage of radiation per fraction and final average hearing threshold.

AHT deterioration was not associated with age (p=0.506), tumor stage (p=1.000) presence of previous hearing loss (p=1.000), diabetes mellitus (p=1.000) hypertension (p=0.961), loop diuretics (p=1.000) or ≥2 comorbidities (p=0.491). Bone conduction threshold deterioration at 4000Hz frequency and air conduction threshold deterioration at 8000Hz frequency did not correlate with radiation dose (p=0.539 and p=0.068), weeks of treatment (p=0.452 and p=0.683) or fractions (p=0.877 and p=0.502). To identify possible predictors of the final average hearing threshold, a simple linear regression was performed, and a correlation was observed between final AHT and dosage of radiation per fraction (p=0.006; CI: 6.959-37.297). Thus, for each increase of 1 Gy per fraction there was an increase of 22.13dB in the final AHT (Figure 4).

DISCUSSION

The growing trend toward the use of organ preservation schemes, coupled with increased overall survival of patients with cancer of the larynx and hypopharynx is reflected in the increased diagnosis and management of radiotherapy-associated complications. The dose and irradiation fields depend on location, size and stage, both T and N.[6] In early-stage tumors (T1 and T2, N0 and N1) of the larynx, the ear is usually not included in the irradiation field because the upper limit is the thyroid notch.[6] However, in advanced-stage tumors, the radiation field extends and the total dose increases, increasing complications and the potential for ototoxicity, especially in the treatment of bulky jugulo-digastric adenopathies, even with the use of techniques such as intensity-modulated radiotherapy.[3,7] In the study by Ondrey et al, the maximum radiation dose applied to the cochlea did not exceed 40 Gy in patients with advanced-stage laryngeal and hypopharyngeal tumors treated with a minimum total dose of 70 Gy.[7] The systematic review by Mujica-Mota et al states that the minimum ototoxic radiation dose applied to the ear in adults is 35 to 40 Gy, and the incidence of sensorineural hearing loss seems to be proportional to the radiation dose.[5] In the present study, only the total radiation dose was considered, and significant deterioration of average hearing thresholds was observed in about 1/3 of the ears, similarly to what was reported in the studies by Upadhya et al and Bhandare et al.[2,4] Contrary to what was reported in the aforementioned studies, this effect did not correlate with advanced tumor stages, but rather with the increase in radiation dose per fraction.

Although our data suggest an ototoxic effect of RT across the frequency spectrum, it was more significant at frequencies ≥4000 Hz, similar to the literature.[8,9] In fact, radiation-induced damage is more pronounced in the basal spira of the cochlea, explained by the smaller amount of outer hair cells in this location.[9,10] The study by Yilmaz et al concludes that the use of otoacoustic emissions may be a more reliable method for early detection of permanent deterioration at high frequencies and predictor of patients at high risk for developing late-onset hearing loss.[10] The present study does not allow inferring data about the timing for the development of hearing loss or about its persistence, given the limited sample and short follow-up, but the literature is controversial. In the study by Wang et al, patients developed sensorineural hearing loss at 3 months after radiotherapy, which progressed over the follow-up period, while in the study by Wakisaka et al, it occurred between the third and tenth year after radiotherapy, with a mean of 7.1 years.[9,11]

Regarding potential confounders, both age and the existence of previous hearing loss seem to directly increase the risk of sensorineural hearing loss.[5,9] However, this was not the case in the present study, probably justified by the short follow-up time, as reported by Wang et al.[9] As reported in the literature, the presence of comorbidities

such as diabetes mellitus or hypertension did not correlate with threshold deterioration.[5]

Most patients had non-significant mild sensorineural hearing loss (<10 dB), mainly unilateral, and therefore prosthetic rehabilitation was not performed. When it occurs suddenly, corticotherapy seems to be beneficial in some patients by reducing edema and inflammation in the inner ear caused by RT.[3] Additionally, by promoting cellular and vascular repair mechanisms, hyperbaric oxygen therapy may be performed, with greater success in patients under 50 years of age.[3] In terms of prosthetic rehabilitation, moderate losses can be easily corrected with air conduction hearing aids, while deep bilateral losses/cophosis should be rehabilitated with cochlear implants.[3] However, the risk of auditory nerve function loss caused by radiotherapy must be taken into account, as well as inner ear fibrosis due to vascular damage, which may begin 3 months after treatment.[3]

The limitations of this article are related not only to the fact that this is a retrospective study, but also to the small number of patients in the sample, and the different follow-up times due to loss of follow-up that conditioned some heterogeneity of the timing of audiometric evaluation.

CONCLUSION

About half of the patients had final AHT deterioration, proving, on the one hand, the radiotherapy-associated sensorineural hearing loss, while emphasizing the need for long-term follow-up protocols for early auditory rehabilitation of these patients. These conclusions, despite being the result of an observational study with a small and heterogeneous sample, may be validated in a larger multicenter study with serial assessments and longer follow-up periods.

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