

# Radiotherapy-Induced Hearing Loss in Patients with Laryngeal and Hypopharyngeal Carcinomas

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## ABSTRACT

*The purpose of this study was to investigate a hypothesized correlation of development of a sensorineural hearing loss and radiotherapy in patients with laryngeal and hypopharyngeal carcinoma. This prospective study included a total of 50 patients, which after strict exclusion criteria (audiologic problems before RT, primary tumors of the auditory system, spread of the primary tumor to any part of the auditory system) resulted in 23 analyzed patients, ranging between 50 and 76 years of age, with a mean age of 60. Audiometry measuring frequency-specific thresholds was performed in three time points: one month before radiotherapy, one and six months after radiotherapy. A significant statistical difference in hearing thresholds after radiotherapy was found in 6 out of 23 patients. An obvious tendency towards hearing loss without statistical significance at 250 and 4000 Hz was found for a whole tested population ( $p \leq 0.3$  with Bonferroni correction). Observed tendency towards hearing loss after radiotherapy of laryngeal carcinoma was related to side of the tumor and less severe when chemotherapy was not added as adjuvant therapy. These results should help to decrease a rate of hearing loss by careful planing of ear protection, by using observed frequencies as relevant markers of hearing loss and by reconsidering adjuvant chemotherapy during radiotherapy of laryngeal carcinoma.*

**Key words:** hearing loss, laryngeal carcinoma, hypopharyngeal carcinoma, radiotherapy, ear protection

## Introduction

Treatment options for head and neck cancers depend upon the size, location and spread of the tumor. Apart from operative procedures, radiotherapy (RT) is a commonly used and often unavoidable method in the treatment of nasopharyngeal, hypopharyngeal and laryngeal carcinoma. Unfortunately, a complex anatomy and location of a tumor often leads to exposure of external, middle and/or inner ear to radiation, which may consequently result in a conductive and/or sensorineural hearing loss (SNHL)<sup>1,2</sup>.

Despite some already performed studies concerning RT-induced ototoxicity in tumors of nasopharynx/hypopharynx<sup>3,4</sup>, a study focused on correlation of radiation therapy of laryngeal carcinoma and hearing loss is missing in the literature. Moreover, we lack information about possible correlation of dose, protocol for RT and loss in particular frequencies.

The aim of this study was to focus on patients with laryngeal carcinoma treated by adjuvant RT and to evaluate the incidence of hearing loss after RT protocols for laryngeal carcinoma. Using a spectrum of audiometric parameters we showed that a dose and protocol used for radiation therapy of laryngeal carcinoma leads to an obvious tendency towards hearing impairment.

## Materials and Methods

### Patients

This study started with 50 patients collected in a period from 2004 to 2008 at our Department. Exclusion criteria which reduced our sample to 23 were as follows: audiologic problems before RT, primary tumors of the auditory system, spread of the primary tumor to any part of

the auditory system, and the follow-up period less than 6 months. All patients were males ranging in age from 50 to 76 years with the median value of 60.

After surgical removal of the tumor, patients were treated with 2D conventional radiotherapy by two lateral opposed fields with a matching anterior lower neck portal, with a 6 MeV electron beam (Mevatron X). The radiation tumor dose was ranging from 50 to 64 Gy, depending of size and location of tumor and status of regional lymph nodes. The spinal cord and ears were shielded by additional 9–12 MeV electron beam. Patients were treated with daily fractionation dose of 2 Gy. No other therapy (e.g. chemotherapy) was included.

### *Hearing evaluation*

Hearing evaluation was performed before, 1 month after and 6 months after irradiation. In this way we grouped our data in three dependant groups for statistical analyses. Audiological evaluation of bone conduction at 250, 500, 1000, 2000, 4000 and 8000 Hz was used for standard estimation of the cochlear damage degree. Audiograms were performed for the right and left ear, independently of one another (Hortman AC 40). Measurements were done before RT, at the end of treatment, and 2 to 6 months after radiotherapy. Pure tone thresholds were investigated in a soundproof room by standard protocols. Clinically significant hearing loss was defined as an increase of the hearing threshold of more than 15 dB in two consecutive measurements conducted at least 6 months apart.

Patients which developed signs of conductive hearing loss (e.g. otitis media) were excluded from this study.

### *Statistical analysis*

Statistical analyses of the data were performed using the IBM SPSS for Windows, version 20. The loss of hearing in all frequencies was normally distributed according to Kolmogorov-Smirnov test. The following parametric test were used for clinical data: GLM Repeated Measures analyzes of related dependent variables and the Paired-Samples T-test procedure for comparison the means of two variables for a single group. Result are significant for  $p \leq 0.05$ , using Bonferoni correction and multiple comparison.

## **Results**

In order to analyse a hypothesized correlation between radiation therapy for carcinoma of larynx and SNHL, we analyzed 23 patients in three time points: before, one month and six months after applied radiation therapy. When compared before and one month after radiation therapy, no single case of SNHL was found. However when the same patients were tested 6 months after radiation therapy, SNHL was found in 6 out of 23 or 26% of the patients ( $p \leq 0.5$ ) Four patients had bilateral hearing loss, but the loss was more prominent on the side of the lesion. In two patients which exhibited unilateral

hearing loss, it was found on a side of tumor, i.e. on a side where radiation therapy was primarily applied. Tables 1a and 1b show the hearing threshold levels for the affected and unaffected ears; hearing thresholds of the unaffected and affected ear for three treatments of study group. An obvious tendency towards significant hearing loss was observed at tumor side for frequencies 250 and 4000 Hz. Presented data were divided into three groups: pretreatment group before radiotherapy, posttreatment group one month after radiotherapy, and posttreatment group six months after radiotherapy. The mean threshold values were higher in both posttreatment groups for both ears. When all 23 patients were fused, no statistical difference in hearing thresholds was observed. However an obvious tendency towards hearing loss on a tumor side at 250 and 4000 Hz between pretreatment group and posttreatment group six months after RT (Table 1a).

## **Discussion and Conclusion**

To the best of our knowledge this is the first study which analyzed hearing loss as a consequence of radiation therapy without chemotherapy after treatment of carcinoma of larynx. Carcinoma of larynx represents around 5% of all tumors in human, but with incidence steadily increasing and surprisingly, with unchanged or even decreased survival rate in the last decades<sup>5</sup>. Thus there is a need for improvement of current therapeutic options and a tendency towards increased agresivness in order to fight this tumor with generally bad prognosis.

One of the most important therapeutic options for laryngeal carcinoma is radiation therapy. Due to the high tumor agresivness, a current protocol includes two lateral opposed fields with a matching anterior lower neck portal, with a 6 MeV electron beam (Mevatron X). The radiation tumor dose is ranging from 50 to 64 Gy.

Side effects caused by radiation therapy in the region of ears are manifested with skin fibrosis, nerve palsy and two kinds of hearing impairment: conductive HL in outer and middle ear or SNHL due to auditory nerve and cochlea damage<sup>6,7</sup>. When we analyzed 8 frequencies, ranging between 250 and 8000 Hz, in three time points, before, one month and six months after of received radiation therapy, it was obvious that in all frequencies there was a trend towards increase of hearing thresholds trough time. Nevertheless, two modalities of hearing impairment were observed: one, in which increase in the threshold was constant and another in which significant impairment occurred between 1 and 6 months after received radiation therapy. For example, a constant increase in hearing threshold was observed in 250, 4000 and 8000 Hz with a statistic significance reached in 250 and 4000 Hz. On a contrary, on 1000, 1500 and 2000 Hz impairment was observed only between 1<sup>st</sup> and 6<sup>th</sup> month after received radiation therapy and a statistic significance was reached only at 1000 Hz.

Up to now, several studies, mostly on patients with nasopharyngeal carcinoma and few studies with mixed laryngeal and nasopharyngeal tumor patients, in combi-

**TABLE 1A**  
HEARING THRESHOLDS OF THE UNAFFECTED EAR FOR A WHOLE GROUP IN THE THREE TIME POINTS.

Frequency (Hz)	Hearing threshold, $\bar{X} \pm SD$ , dB hearing loss (N=23)			
	Pretreatment (1)	Posttreatment after 1 mont (2)	Posttreatment after 6 months (3)	p* (1)-(3)
250	17.8±12.1	18.7±13.1	19.3±14.9	0.259
500	18.9±13.4	20.7±14.6	20.9±16.7	0.258
1000	22.8±13.6	23.7±16.7	23.7±17.4	0.755
1500	25.0±16.7	25.4±16.2	27.4±18.6	0.486
2000	27.2±19.8	28.5±16.1	31.5±22.1	0.278
3000	36.5±19.7	39.1±17.2	41.3±20.4	0.197
4000	50.2±21.7	51.1±19.9	54.8±20.1	0.250
8000	54.1±22.2	56.7±26.2	59.3±27.4	0.148

\* t-test for dependent samples

**TABLE 1B**  
HEARING THRESHOLDS OF THE AFFECTED EAR FOR A WHOLE GROUP IN THE THREE TIME POINTS.

Frequency (Hz)	Hearing threshold, $\bar{X} \pm SD$ , dB hearing loss (N=23)			
	Pretreatment (1)	Posttreatment after 1 mont (2)	Posttreatment after 6 months (3)	p* (1)-(3)
250	16.5±8.5	18.9±13.0	21.5±15.1	0.036
500	19.1±11.4	20.2±12.3	22.6±15.0	0.133
1000	22.4±14.4	21.7±13.1	25.4±16.1	0.110
1500	27.6±17.3	25.7±15.2	28.3±18.8	0.700
2000	33.3±21.2	31.5±18.9	34.3±23.2	0.636
3000	41.1±21.3	43.5±20.0	47.2±24.5	0.081
4000	54.1±21.1	58.3±23.8	61.7±25.8	0.033
8000	59.8±25.3	62.6±27.4	64.8±27.1	0.113

\* t-test for dependent samples

nation with chemotherapy have been performed<sup>8–16</sup>. It became obvious that hearing impairment is dependant on location of the tumor and dose of radiation. In his prospective study Liberman et al. reported a hearing loss followed administration of RT and chemotherapy (cisplatin) in 36% (4/11) patients treated for laryngeal/ hypopharyngeal carcinoma<sup>13</sup>. A higher incidence of SNHL in Liberman study (36% vs. 23%) could be explained by additional toxicity of chemotherapy used in combination with RT. In a similar study Lacava et al. reported 43% of patients with laryngeal carcinoma (treated by cisplatin) experienced HL<sup>14</sup>. In this way, we can confirm that combination of RT and chemotherapy in patients with laryngeal carcinoma brings significantly increased risk of hearing impairment. The same findings were reported by

Chen<sup>3</sup>, Xiao<sup>4</sup> and Hitchcock<sup>15</sup> in nasopharyngeal carcinoma treated by RT and chemotherapy.

The pathophysiological background of SNHL is only partly explained. According to Low and Fong SNHL mostly develops due to vascular effects, such as atrophy of the stria vascularis of the cochlear duct<sup>17</sup>. Decreased possibility for tissues regeneration is probably a reason why SNHL is more likely to be completely irreversible in older patients.

In conclusion, these results should help to decrease a rate of hearing loss by careful planing of ear protection, by using observed frequencies as relevant markers of hearing loss and by reconsidering adjuvant chemotherapy during radiotherapy of laryngeal carcinoma.

## REFERENCES

1. CONNOR NP, COHEN SB, KAMMER RE, SULLIVAN PA, BREWER KA, Int J Radiat Oncol Biol Phys, 65 (2006) 262. — 2. YILMAZ YF, AYTAS I, AKDOGAN O, SARI K, SAVAS ZG, Otol Neurot. 29 (2008) 132. — 3. CHEN WC, JACKSON A, BUDNICK AS, PFISTER DG, KRAUS DH, Am Cancer Society, 106 (2006) 820. — 4. XIAO WW, HUANG SM, HAN F, WU SX, LU LX, LIN CG, DENG XW, LU TX, CUI NJ, ZHAO C, Cancer, 117 (2011) 1874. — 5. PANTEL M, GUNTINAS-LICHIUS O, HNO, 60 (2012) 32. — 6. PLOWMAN PN, Int J Radiat Oncol Biol Phys, 52 (2002) 591. — 7. HONORE HB, BENTZEN SM, MOLLER K, GRAU C, Radioth oncol, 65 (2002) 9. — 8. BHANDARE N, ANTONELLI PJ, MORRIS CG, MALAYAPA RS & MENDENHALL WM, Int J Radiat Oncol Biol Phys, 67 (2007) 469. — 9. PAN CC, EISBRUCH A, LEE JS, SNORRASON RM, HAKEN RKT, Int J Radiat Oncol Biol Phys, 61 (2005) 1393. — 10. HERRMANN F, DORR W, MULLER R, HERRMANN T, Int J Radiat Oncol Biol Phys, 65 (2006) 1338. — 11. KWONG DL, WEI W, SHAM JS, Int J Radiat Oncol Biol Phys, 36 (2006) 281. — 12. ZUUR CL, SIMIS YJ, LAMERS EA, HART AA, DRESCHLER WA, Int J Radiat Oncol Biol Phys, 74 (2006) 490. — 13. LIBERMAN PHP, SCHULTZ C, SHMIDT MV, GOMEZ G, CARVALHO AL, Arch Otolaryngol Head Neck Surg, 130 (2004) 1265. — 14. LACAVA JA, FERREYRA R, LEONE BA, LOSADA C, ELEM JL, Cancer J Sci Am, 2 (2006) 46. — 15. HITCHCOCK YJ, TWARD JD, SZABO A, BENTZ BG, SHRIEVE DC, Int J Radiat Oncol Biol Phys, 73 (2009) 779. — 16. WAKISAKA H, YAMADA H, MOTOYOSHI K, UGUMORI T, TAKAHASHI H, HYODO M. Auris Nasus Larynx. 38 (2011) 95. — 17. LOW WK, FONG KW, Larynx, 25 (1998) 21.

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## GUBITAK SLUHA UZROKOVAN RADIOTERAPIJOM U PACIJENATA S LARINGEALNIM I HIPOFARINGEALNIM KARCINOMOM

### SAŽETAK

Cilj ove studije je bio sitražiti pretpostavljenu vezu između nastanka snzoneuralnog gubitka sluha i radioterapije u pacijenata s laringealnim i hipofaringealnim karcinomom. Ova prospektivna studija je uključila 50 pacijenata, koji su nakon strogih kriterija eliminacije (audiološki problemi prije radioterapije, primarni tumor organa sluha, širenje tumora na organ sluha) svedeni na 23 analizirana pacijenta u dobi između 50 i 76 godina (prosjeak 60). Audimetrijska mjerenja pragova po frekvencijama su rađena u tri vremenske točke: jedan mjesec prije radioterapije, jedan mjesec nakon i šest mjeseci nakon radioterapije. Statistički značajan gubitak sluha je nađen u 6 od 23 pacijenta. Očigledna, iako ne i statistički značajna tendencija gubitku sluha na frekvencijama od 250 i 4000 Hz je nađena u cijeloj populaciji. ( $p < 0,3$  bonferronijeva korekcija). Opažen gubitak sluha nakon radioterapije laringealnog i hipofaringealnog karcinoma se javio na strani tumora i značajno manji u slučaju kada nije korištena kemoterapija. Ovi rezultati mogu pomoći da se smanji gubitak sluha u navedenih pacijenata. To se može postići boljom zaštitom organa sluha tijekom radioterapije, korištenjem opisanih frekvencija kao pouzdanih biljega gubitka sluha i kao izbjegavanjem dodatne kemoterapije tijekom radioterapije karcinoma larinsa i hipofarinksa.