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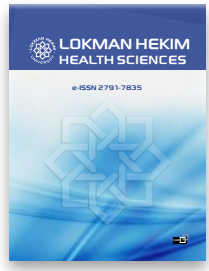

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ORIGINAL ARTICLE

Voice and Hearing Outcomes in Nasopharyngeal Cancer Survivors: A Cross-Sectional Evaluation

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Abstract

Introduction: The study aims to evaluate and compare the voice and hearing outcomes in nasopharyngeal cancer survivors treated with radiotherapy (RT) or chemoradiotherapy with a healthy control group.

Methods: This cross-sectional study recruited 21 patients with a history of nasopharyngeal carcinoma (NPC) who received RT or chemoradiotherapy and 19 control subjects matched for age. Voice evaluation was performed using perceptual and acoustic measures, and hearing function was assessed using pure tone audiometry.

Results: The NPC group exhibited significantly poorer voice quality, as indicated by higher perceptual scores (GRBAS scale), higher self-reported voice handicap (voice handicap index - 10 scale), and increased frequency perturbation (%jitter) compared to the control group. Significant differences were also observed in other acoustic parameters, including fundamental frequency, amplitude perturbation (% shimmer), and noise-to-harmonic ratio. Hearing loss was more prevalent in the nasopharyngeal cancer group, particularly at high frequencies. Some correlations were observed between certain acoustic voice parameters and hearing thresholds, particularly in the nasopharyngeal cancer group. However, a consistent pattern across all parameters was not evident.

Discussion and Conclusion: Nasopharyngeal cancer survivors treated with RT or chemoradiotherapy experience significant voice and hearing impairments compared to healthy controls. These findings highlight the importance of routine voice and hearing evaluations for this patient population.

Keywords: Cancer; Hearing; Nasopharynx; Radiotherapy; Voice

The nasopharynx is a unique anatomical site that influences both hearing and voice, and its disorders can disrupt communication by altering any or both of these two functions. Different nasopharyngeal pathologies are studied for problems of hearing and voice, and examining these in nasopharyngeal cancer survivors could add to our

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knowledge to understand the physiology of hearing, voice, and the relationship between them.

Nasopharyngeal carcinoma (NPC) is a relatively uncommon cancer and 70% of the cases are seen in East and Southeast Asia, while the incidence rate is 0.4/100,000 in the Caucasian population.[1] The primary treatment for NPC is radiotherapy (RT), often combined with chemotherapy (CT) based on the stage.[2] These treatments, while effective, pose challenges due to their impact on auditory and vocal functions. Communication problems affecting quality of life are observed in NPC patients, stemming either from the tumor itself or therapy side effects. The effects of RT on the external ear, middle ear, and inner ear can result from changes such as fibrosis and neural loss following cell damage.[3,4] Side effects occurring 90 days after the end of RT are defined as late side effects.[5] In addition, because RT targets both the primary nasopharyngeal site and the adjacent neck regions to address potential lymphatic metastases, RT-induced tissue damage often extends across broader anatomical areas. The most common side effect of neck irradiation is xerostomia, a result of diminished salivary function, which can significantly alter the human voice.[6]

Most of the studies on NPC survivors are focused on hearing problems. In general, the studies of the voice of these patients are limited to a small number of cases in non-laryngeal head-and-neck cancer studies. It is recognized that the voices of post-RT non-laryngeal cancer patients may be compromised more than the voices of post-RT early glottic cancer patients.[7] There is a need for voice evaluation data according to anatomical localization after RT/completed RT (CRT), as discussed in the literature[8] in terms of nasopharyngeal localization.

There are several possible explanations for how the RT affects voice in NPC patients. Radiation may affect either the phonation changing the biomechanical properties of the vocal folds or the resonance by altering the whole vocal tract.[9] Furthermore, the side effects involving the cortical brain and tracts down to the cranial nerves, although thought to be clinically rare previously, have been shown to be quite effective in voice changes in NPC patients.[10] In addition, it is established that hearing loss (HL) affects the voice in different patient groups.[11,12]

Today, with more tailored treatment modalities and the increase in successful treatments, there is an increase in the number of survivors seeking help for their voice and/or hearing problems. Even after the successful treatment of NPC, the problems affecting the quality of life of these individuals are observed.[13] Successful treatment of NPC is achieved. To reach the level of success in the field of rehabilitation, especially for voice and hearing problems, studies need to be done to clarify the problems of the survivors.

The study's purpose is to answer the following clinical question: "Among patients with post-RT NPC, does the voice characteristics and hearing, when compared with a group of individuals without any RT history, are different?" It is hypothesized that long-term voice and hearing outcomes after treatment of NPC subjects are different from the control subjects. This study aimed to estimate and compare clinician- and patient-reported voice perception, acoustic parameters, and audiometric findings between subjects who received RT for NPC and those who did not. In addition, the effects of HL on the aforementioned voice parameters were investigated and compared between the two groups using these data.

Materials and Methods

The study was conducted as a cross-sectional evaluation to compare voice and hearing outcomes between NPC survivors and a healthy control group. The sample for the study group (NPC group) consisted of subjects who completed curative-intent RT or chemoradiotherapy during the specified study period and presented for long-term follow-up and were examined for follow-up visits in the otorhinolaryngology outpatient clinic of a tertiary hospital. All outcome measures, including voice analysis and audiologic assessments, were collected at a single point in time during these follow-up visits. To minimize selection bias, all consecutive patients who visited the clinic during the study period and met the inclusion and exclusion criteria described below were included in this cross-sectional study. Hospital staff and patient companions, who matched this study group in terms of age, and who had no complaints/signs related to hearing and voice problems before, were recruited as the control group. This study was approved by the Ankara Yıldırım Beyazıt University (Date: 21.11.2018, Decision no: 12). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data collection of the study was conducted between November 2018 and January 2020. Individuals in both the study group and the control group were included voluntarily by explaining the purpose of the study. The data were collected after obtaining their informed consent. All consecutive NPC survivors who had RT or CRT

at the tertiary care center were screened initially. To ensure a homogenous study group and minimize confounding factors, specific selection criteria were applied. The inclusion criteria for the study group were:

- Being male
- Aged 19–55 years[4]
- Being a non-smoker or having quit smoking for at least 1 year at the time of assessment
- Being at least 3-month post-treatment.

The criteria for exclusion from the study group were:

- History of surgical treatment for NPC
- History of chronic otitis media before the diagnosis of NPC
- History of HL noticed/diagnosed before the disease (except for the initial otological signs and symptoms leading to the NPC diagnosis)
- History of additional treatment for recurrent/residual cancer after initial diagnosis and treatment
- Vocal fold mobility disorder detected by routine nasopharyngolaryngoscopy in the follow-up examination

The criteria for exclusion from both groups were:

- Being female
- Age outside 19–55 years range
- Current smoking (or has quit in the last year)
- History of having comorbid diseases (systemic diseases, such as diabetes mellitus) or using medications that will cause hearing or voice problems
- History of otological intervention (myringotomy, pressure equalizing tube placement, myringoplasty/tympanoplasty, or further otological/neuro-otological surgery)
- Having any experience using a hearing aid
- Any complaint/diagnosis related to voice, history of voice surgery, or comorbid condition that may affect voice (including history of thyroidectomy, basal ganglia diseases).

To compare the NPC group with control subjects in terms of acoustic analysis, subjects with vocal fold mobility disorders were excluded, as these disorders cause asymmetries in vocal fold tension that may affect pitch, vocal fatigue, and intensity of phonation. The ages of the individuals in the study and control groups; the stages of the individuals in the study group at the time of diagnosis, the status of receiving RT and/or CRT, the status of receiving additional CT, the time from treatment to the date of evaluation in months, having a complaint of "dry mouth" (xerostomia grading according to Common Terminology Criteria for Adverse Effects Version 3 – CTCAE v3.0) were recorded.[5]

Voice Analysis

The procedures and the tasks expected to be completed were explained to the subjects by the researcher, with examples. Voice samples of subjects were obtained in the audiometric booth with the "Audio Technica AT2005USB dynamic microphone" and "Audacity v.2.2.0 software" program. The recording format is uncompressed digital recording (.wav extension), sampling rate 44 100 Hz, quantization (bit resolution) 16 bit, and recorded in mono-channel. The distance between the microphone and the mouth was recorded as 5 cm. In the booth, after a short conversation about their daily activities, subjects were asked to sit upright but in a comfortable position, breathe comfortably, and read the first paragraph of the "Diyet Passage," a standard phonetically balanced Turkish text for voice studies, at a comfortable pitch and loudness.[14] After that, they were asked to pronounce the open-mid back unrounded vowel (/ʌ/) for at least 3 seconds at modal phonation (typical pattern of vocal fold vibration used in normal speech production, characterized by balanced tension and airflow). After three repetitions, the recording, which was thought to best reflect the individual's voice, was kept in the computer for acoustic analysis.

After taking samples for voice analysis, individuals who were taken out of the cabin were asked to fill in the printed version of the voice handicap index-10 (VHI-10) scale, of which Turkish validity and reliability had been evaluated before.[15] VHI-10 measures the patient's subjective assessment of voice-related quality of life. The total score was recorded.

Perceptual voice evaluation was made by the GRBAS scale based on the passage readings, and the results were recorded. The GRBAS scale evaluates voice quality based on five perceptual parameters. These were rated by a researcher experienced in voice studies for over 10 years.

Audio recording samples of the vowel /ʌ/ were analyzed in a computer using the "Customized Praat" version[16] based on Praat software (http: www.fon.hum.uva.nl/praat/, version 4.8, Paul Boersma and David Weenik, Phonetic Sciences Department, University of Amsterdam). A mid-2-second segment of each sample was analyzed. Fundamental frequency (F0), jitter and shimmer percentage values of individuals, and the average Noise-Harmonic ratio (NHR) were calculated.

Otological Examination and Audiological Tests

An otoscopical examination was performed before the audiological tests. It was confirmed that no pathology in the external ear canal that would affect the audiological test result, and there was no tympanic membrane perforation. An acoustic immittance test was performed with the Maico MA 34 Tympanometry device with a 226 Hz probe tone. Pure tone audiometry was performed in a soundproof audiometry booth with the Resonance r37a Audiometer device. Airway hearing was assessed in the range of 500–6000 Hz using supra-aural headphones (TDH-39). Bone conduction hearing measurement was assessed in the range of 500–4000 Hz with a B71 bone transducer/P-333 head circle. Pure tone averages (PTA) were calculated by taking 500, 1000, 2000, and 4000 Hz hearing threshold averages. Degree of HL was classified according to a scale previously defined for late complication classification.[17] The minimum of the air conduction hearing thresholds (and PTA) of both ears was selected for each subject to make a correlation analysis between the hearing threshold level and the acoustic analysis data of the subject's voice.

Statistical Analysis

Descriptive statistics were given as median, interquartile range, minimum, maximum, frequency, and percentage. The conformity of continuous variables to the normal distribution was evaluated with the Shapiro–Wilk test. Comparisons between groups of continuous variables were made with Mann–Whitney U-test in the independent groups.

A primary methodological consideration was the potential interdependence of data from two ears of the same subject. To maintain the statistical assumption of independent observations for intergroup comparisons, a two-step approach was adopted. First, hearing thresholds from all ears were presented for descriptive purposes only. Second, for all analytical intergroup comparisons and correlation analyses, the better ear, defined as the ear with the lower PTA, was selected for each subject (patient and control groups). The linear relationship between the variables was evaluated with Spearman's correlation test. A $p<0.05$ was accepted for statistical significance. Statistical analysis was done with IBM Statistical Package for the Social Sciences version 21.0 (IBM Corp. Released 2012. Armonk, NY, USA) program.

Results

Twenty-one subjects who received NPC treatment (RT or CRT) in the study group and 19 subjects in the control group participated in the study. All subjects were male. The median age of the study group was 46 (21–55) years, while the median age of the control group was 45 (18–55) years. The median time from the end of treatment to the evaluation date of the subjects in the study group was 48 (3–225) months. All subjects in the study group had grade 1 xerostomia described as "Symptomatic (e.g., dry or thick saliva) without significant dietary alteration," according to the CTCAE v5.0. None of the control subjects had dry mouth or thick saliva complaints.

At the time of diagnosis, 76.2% of the subjects (n=16) in the study group were recorded as the advanced stage (Stages III, IVa, IVb; 57.1%, 14.3%, 4.8%, respectively). Five subjects (23.8%) were recorded as Stage II, and there was no Stage I subject. Of all cases in the study group, 71.5% (n=15) received concurrent CT, and 19% (n=4) received adjuvant CT. Two subjects (9.5%) did not receive any CT. A total of 240 mg/m2 cisplatin were administered as the CT agent, divided into weekly doses, to the subjects receiving treatment in the center where the study was conducted.

As the number of subjects falling into some stages was low, the voice evaluation and hearing evaluation data of the study group were not statistically examined according to the NPC stages. Since the vast majority of patients received concomitant CRT and the number of subjects in the RT-only and adjuvant CRT subgroups was insufficient for a separate statistical comparison, the study group was evaluated as a single entity regardless of the specific treatment modality.

All patients were treated with intensity-modulated RT. Gross tumor volume for the primary tumor and involved cervical lymph nodes was delineated using positron emission tomography-computed tomography and MRI. The clinical target volume (CTV) encompassed the GTV plus a 1–1.5 cm margin, the entire nasopharyngeal region, and all lymph-node areas with metastatic involvement. Planning target volumes were generated by expanding the CTV by 0.5 cm. The prescribed radiation dose was 69.96 Gy (2.12 Gy/fraction, once daily) for the GTV and 54–60 Gy (1.63–2 Gy/fraction, once daily) for the CTV. In addition, organs at risk – including the brainstem, spinal cord, parotid glands, eyes, optic chiasm, optic nerves, cochleae, middle ear, and inner ear structures – were contoured on the planning CT.

The voice evaluation data of the study group and the control group and the statistical significance of the difference between the data are shown in Table 1. Perceptual assessment (GRBAS scale scores), voice self-assessment (VHI - 10 scores), and acoustic analysis data of individuals were statistically significantly different between the two groups. To speak with the normative values, the VHI-10 score was higher than 11 (which is the cut-off value of the pathological finding), in

Table 1. Voice evaluation data of subjects

	NPC group (n=21) median (IQR) [min-max]	Control group (n=19) median (IQR) [min-max]	p
GRBAS	4 (3)	2 (2)	0.002
	[2–13]	[0–7]	
VHI – 10	9 (19)	1 (6)	0.004
	[0–38]	[0–21]	
F_0	122.61 (38.31)	135.03 (17.87)	0.039
	[96.6–219.8]	[105.9–211.9]	
% jitter	0.490 (0.485)	0.271 (0.151)	0.000
	[0.21–3.90]	[0.15–2.01]	
% shimmer	1.879 (1.543)	1.514 (0.734)	0.039
	[0.94–14.90]	[0.67–6.20]	
Mean NHR	0.0079 (0.0082)	0.0033 (0.0037)	0.003
	[0.002–0.274]	[0.001–0.048]	

NPC: Nasopharyngeal carcinoma; IQR: Interquartile range; Min: Minimum; Max: Maximum; GRBAS: Grade roughness breathiness asthenia scale score; VHI-10: Vocal handicap index – 10 score; F_0: Fundamental frequency; NHR: Noise-to-harmonic ratio.

10 of 21 individuals in the study group. In the control group, 3 out of 19 individuals had a VHI-10 score higher than 11. The NPC group exhibited significantly higher jitter values compared to controls (p<0.001; Table 1). We could not compare our acoustic measurements to any cut-off points defined by previous literature data, which would vary with the recording conditions and individual factors (age, sex, race, ethnicity, dialect, geographic location).[18]

Air conduction (AC) PTA was <25 dB in 18 of 42 ears in the study group. Mild HL (AC 26–40 dB) was detected in a total of 14 ears (sensorineural HL in 5 ears, conductive HL in 5 ears, and mixed HL in 4 ears). Moderate HL (AC 41–55 dB) was detected in a total of 8 ears (sensorineural HL in 4 ears and mixed HL in 4 ears). Severe HL (AC 56–70 dB) was not detected. There was sensorineural HL in two ears with profound HL (AC >71 dB).

According to the HL type, there was sensorineural HL in 11 ears, conductive HL in 5 ears, and mixed HL in 8 ears.

HL (>25 dB air-conduction threshold) was detected at low-frequency hearing thresholds (500–1000–2000 Hz) in 20 (47.6%) of 42 ears of study subjects. HL at high-frequency hearing thresholds (4000–6000 Hz) was detected in 37 (88%) of them.

In the control group, AC was found to be <25 dB in 36 of 38 ears, and mild mixed HL is present in the other two ears.

Air and bone conduction thresholds and PTA were depicted for the ears of two groups in Table 2.

Table 2. Pure tone audiometry data of the ears in dB

	NPC group (42 years) median (IQR) [min-max]	Control group (38 years) median (IQR) [min-max]
A500 Hz	15 (20)	10 (6)
	[0–65]	[0–40]
A1000 Hz	20 (23)	10 (10)
	[0–65]	[0–25]
A2000 Hz	20 (21)	10 (11)
	[0–70]	[0–35]
A4000 Hz	47.5 (40)	22.5 (25)
	[5–100]	[0–65]
A6000 Hz	52.5 (36)	22.5 (30)
	[10–110]	[0–60]
B500 Hz	10 (20)	5 (10)
	[0–45]	[0–40]
B1000 Hz	15 (15)	10 (6)
	[0–45]	[0–20]
B2000 Hz	12.5 (20)	5 (30)
	[5–60]	[0–30]
B4000 Hz	40 (30)	20 (25)
	[5–75]	[0–60]
Air conduction PTA	27 (21)	15 (10)
	[6–75]	[0–31]
Bone conduction PTA	18.75 (14)	11.25 (10)
	[8–51]	[0–25]

NPC: Nasopharyngeal carcinoma; IQR: Interquartile range; Min: Minimum; Max: Maximum; PTA: Pure tone average; A: Air conduction threshold; B: Bone conduction threshold.

The minimum of the air conduction hearing thresholds (and PTA) of both ears selected for each subject, to represent the better–ear, is shown in Table 3, and is statistically significantly different between the two groups, except for 3 of the 10 parameters.

Correlations between voice evaluation data are shown in Table 4. Both in the study group and control group, GRBAS was correlated with F0, whereas VHI-10 score was correlated with %shimmer and mean NHR. There was also a strong correlation between the GRBAS score and the VHI-10 scores in the NPC group (rs=0.498, p=0.022).

For the association between hearing status and voice, voice parameters were analyzed according to the degree of HL. The distributions of the voice evaluation data were the same across the hearing level degrees in both groups. Further analysis was conducted. The correlations between voice evaluation data and audiometric data are shown in Table 5.

Table 3. The air conduction hearing thresholds (and PTA) of the better ear for each subject in dB

Minimum thresholds (dB)	NPC group (n=21)		Control group (n=19)		p
	Median (IQR) [min-max]	M±SD	Median (IQR) [min-max]	M±SD	
A500 Hz	10 (20)	16.43	5 (5)	7.89	**0.027**
	0–60	14.15	[0–20]	5.84	
A1000 Hz	15 (18)	17.38	10 (10)	7.63	
	0–65	15.05	[0–25]	6.53	**0.012**
A2000 Hz	15 (20)	18.81	10 (10)	10.53	
	0–70	16.65	[0–30]	8.31	0.088
A4000 Hz	40 (43)	44.05	20 (25)	16.46	
	5–95	24.11	[0–55]	14.98	**0.004**
A6000 Hz	45 (35)	47.86	15 (25)	20.00	
	10–110	26.39	[0–15]	16.41	**<0.001**
B500 Hz	10 (8)	11.67	5 (10)	5.26	
	0–35	9.26	[0–15]	4.55	**0.016**
B1000 Hz	10 (10)	12.38	5 (10)	6.32	
	0–45	12.00	[0–15]	4.66	0.088
B2000 Hz	10 (35)	16.19	5 (5)	8.68	
	5–70	14.13	[0–30]	7.23	0.078
B4000 Hz	40 (35)	36.43	15 (20)	19.74	
	5–70	19.31	[0–50]	14.57	**0.005**
Air conduction PTA	21 (19)	25.20	11 (11)	12.79	
	[6–73]	15.70	[0–25]	6.63	**0.002**

NPC: Nasopharyngeal carcinoma; IQR: Interquartile range; Min: Minimum; Max: Maximum; M: Mean; SD: Standard deviation; PTA: Pure tone average; A: Air conduction threshold; B: Bone conduction threshold.

In the NPC study group, there were relations between some frequency parameters and some audiometric thresholds (F0: 1000 Hz, 4000 Hz air conduction thresholds and 1000 Hz bone conduction threshold, %jitter: Minimum PTA, 2000 Hz, 4000 Hz, 6000 Hz air conduction thresholds and 2000 Hz bone conduction threshold), whereas there was no such relationship in the control group.

A relationship was found between the GRBAS score and only 1000 Hz bone conduction thresholds in the NPC study group. No relationship with GRBAS score was found in the control group.

While there was no relationship between VHI-10 scores and audiometric data in the NPC study group, there was a relationship between VHI-10 scores and the following thresholds of the control group: 4000 Hz and 6000 Hz air conduction thresholds and 4000 Hz bone conduction thresholds.

Discussion

This study aimed to investigate the long-term impact of RT on voice characteristics and hearing in patients with NPC. We hypothesized that NPC patients who underwent RT would exhibit significant differences in voice and hearing compared to a healthy control group. This study sought to estimate and compare voice perception (clinician and patient-reported), acoustic voice measures, and audiometric data between individuals with and without a history of RT for NPC, while also investigating the impact of HL on these voice parameters in both groups. Due to the nature of our data, we interpret our findings as a cross-sectional assessment of the presence of voice and hearing impairments in long-term NPC survivors rather than a strict analysis of the long-term impact or temporal progression of RT/CRT. In this respect, we aimed to ensure consistency between our stated aim and the limitations imposed by the study design.

Our findings revealed significant differences in voice characteristics between the NPC group and the control group. Perceptual assessments (GRBAS), patient-reported outcomes (VHI-10), and objective acoustic measures (e.g., jitter, shimmer, NHR) all indicated poorer voice quality in the NPC group.

The relationship between nasal and nasopharyngeal pathologies (allergic rhinitis, adenoid hypertrophy, and the conditions that cause velopharyngeal insufficiency such as cleft palate) and voice disorders has been the subject of many studies.[19,20] It has been determined that diseases of this anatomic site, which is generally accepted as related to the resonance component of the voice, affect not only the resonance but also other components of the voice. Parameters, including F0, which is related to the phonation component of the voice, are found to be affected.[19] Many explanatory mechanisms, from upper respiratory tract reflexes to hyper-functional voice and related problems that develop to compensate for increased intraoral pressure, have been presented as hypotheses. However, it has not been possible to reach a clear judgment on this issue yet.

Even non-cancerous pathologies of the region that is the subject of this study can cause such disorders, while the addition of treatment with side effects such as RT complicates the situation even more.

When compared with normal individuals of the same age and sex, it has been shown that the individuals who have undergone wide-field RT due to non-laryngeal tumors of the head and neck have significant vocal dysfunction.[7,21] When the voice values of individuals who received narrow-field RT directly to the larynx for early-stage glottic tumors and those who received wide-field RT for non-laryngeal

Table 4. Correlations between voice evaluation data

	NPC group (n=21)					Control group (n=19)				
	F_0	%jit	%shim	Mean NHR	GRBAS	F_0	%jit	%shim	Mean NHR	GRBAS
%jit	-0.201					-0.218				
	0.382					0.371				
%shim	0.250	**0.561**				0.242	0.419			
	0.274	**0.008**				0.318	0.074			
Mean NHR	0.049	**0.662**	**0.854**			-0.228	**0.859**	**0.530**		
	0.832	**0.001**	**0.000**			0.347	**0.000**	**0.020**		
GRBAS	0.409	0.352	0.249	0.311		0.455	-0.037	-0.118	-0.287	
	0.065	0.117	0.277	0.170		0.050	0.879	0.631	0.233	
VHI10	0.242	0.115	0.430	0.333	**0.498**	0.289	0.268	**0.784**	0.410	0.064
	0.290	0.621	0.052	0.140	**0.022**	0.231	0.268	**0.000**	0.081	0.795

Spearman's rho (top) and p-value (bottom) are presented in each cell. NPC: Nasopharyngeal carcinoma; IQR: Interquartile range; SD: Standard deviation; GRBAS: Grade roughness breathiness asthenia scale score; VHI-10: Vocal handicap index – 10 score; F_0: Fundamental frequency; NHR: Noise-to-harmonic ratio.

Table 5. Correlations between voice evaluation data and pure tone audiometry data of the better ear

Min. values (dB)	NPC group (n=21)						Control group (n=19)					
	F_0	%jit	%shim	Mean NHR	GRBAS	VHI10	F_0	%jit	%shim	Mean NHR	GRBAS	VHI10
PTA	0.413	**-0.543**	-0.007	0.025	0.068	0.181	-0.264	0.093	0.210	0.197	-0.060	0.251
	0.063	**0.011**	0.975	0.913	0.770	0.431	0.274	0.706	0.389	0.420	0.807	0.299
A500	0.198	-0.431	-0.100	-0.080	0.121	0.245	-0.148	0.131	-0.056	-0.131	0.416	-0.061
	0.390	0.051	0.665	0.729	0.601	0.285	0.547	0.593	0.820	0.594	0.076	0.803
A1000	**0.446**	-0.379	-0.004	0.034	0.278	0.320	-0.309	0.148	-0.105	0.122	0.132	-0.237
	0.043	0.090	0.986	0.885	0.222	0.157	0.197	0.546	0.669	0.618	0.589	0.329
A2000	0.309	**-0.533**	-0.018	-0.058	0.061	0.212	-0.326	-0.067	0.048	0.000	-0.213	0.008
	0.173	**0.013**	0.937	0.801	0.794	0.356	0.173	0.784	0.846	1.000	0.382	0.975
A4000	**0.494**	**-0.515**	0.110	0.065	0.004	0.051	-0.032	0.081	0.332	0.251	0.060	**0.520**
	0.023	**0.017**	0.634	0.781	0.985	0.825	0.896	0.742	0.165	0.299	0.806	**0.022**
A6000	0.356	**-0.610**	-0.129	-0.210	-0.105	-0.054	0.032	0.328	0.411	0.405	0.228	**0.556**
	0.114	**0.003**	0.577	0.361	0.651	0.817	0.897	0.170	0.081	0.086	0.349	**0.014**
B500	0.110	-0.039	0.046	0.089	0.366	0.325	0.014	-0.046	-0.150	-0.156	0.329	0.047
	0.636	0.867	0.842	0.703	0.103	0.150	0.955	0.851	0.539	0.523	0.169	0.849
B1000	**0.502**	-0.135	0.206	0.183	**0.468**	0.268	-0.242	0.130	-0.164	0.166	0.152	-0.071
	0.020	0.558	0.371	0.428	**0.032**	0.240	0.319	0.596	0.501	0.498	0.535	0.772
B2000	0.364	**-0.608**	-0.084	-0.194	-0.077	0.035	-0.215	-0.174	-0.145	-0.120	-0.245	-0.021
	0.105	**0.003**	0.718	0.400	0.739	0.880	0.378	0.475	0.555	0.626	0.311	0.931
B4000	0.428	-0.334	0.131	0.133	0.024	-0.044	0.073	0.130	0.326	0.296	0.091	**0.619**
	0.053	0.139	0.570	0.566	0.917	0.848	0.768	0.596	0.174	0.218	0.713	**0.005**

Spearman's rho (top) and p-value (bottom) are presented in each cell. NPC: Nasopharyngeal carcinoma; IQR: Interquartile range; SD: standard deviation; GRBAS: Grade roughness breathiness asthenia scale score; VHI-10: Vocal handicap index – 10 score; F_0: Fundamental frequency; NHR: Noise-to-harmonic ratio; PTA: Pure tone average; A: Air conduction threshold; B: Bone conduction threshold.

head-and-neck tumors were compared, it was reported that wide-field RT application caused more changes in the voice due to non-laryngeal primary in terms of voice quality.[7]

The most common side effect of NPC treatment is xerostomia. Although not within the RT field, the larynx is exposed to radiation as its proximity to neck structures. Platinum-based

antineoplastic drugs used in locoregionally advanced disease are neurotoxic. CT exacerbates salivary dysfunction, worsening xerostomia.[17] Therefore, the development of xerostomia causes a lack of lubrication, affecting vocal function.

In addition, soft tissue changes such as fibrosis, telangiectasia, atrophy, edema, and lymphatic drainage changes caused by RT affect the vocal tract and extra-laryngeal muscles. The side effects involving the cortical brain and tracts down to the cranial nerves, although thought to be clinically rare previously, have been shown to be quite effective in voice changes in NPC patients.[10] The resulting voice disorders affect the quality of life after treatment by disrupting communication.

In summary, from a voice perspective, the results of this study align with previous studies demonstrating vocal dysfunction following radiation therapy for head-and-neck cancers, particularly in non-laryngeal tumors.[7,9,22] However, our study extends these findings by providing a comprehensive assessment of voice characteristics in a relatively large number of NPC patients.

Furthermore, the NPC group exhibited significantly higher rates of HL compared to the control group. Pure tone audiometry revealed a high prevalence of HL, particularly at high frequencies, in the NPC group. These findings align with prior reports of late auditory complications from RT, including sensorineural and mixed HL.[4,23]

Otological side effects occurring after the treatment of NPC have been classified by many scales. The Radiation Therapy Oncology Group (RTOG) late toxicity classification was made according to air conduction PTA values. The RTOG and other toxicity scales, including LENT-SOMA and the CTCAE, are not fully compatible and show limited consistency with otolaryngology-based HL classifications. Therefore, additional staging systems were applied to assess post-treatment hearing outcomes.[4,17] The observed rates of HL in our study were lower than some previously reported rates. This discrepancy may be attributed to factors such as the inclusion criteria (e.g., age range) and the definition of HL used in this study.

In light of all these data, to be able to evaluate the hearing data after NPC in a healthy way, it would be appropriate to standardize the findings in the studies, to determine the approximate values with prospective studies, and to regularly evaluate the individuals in terms of ear and hearing, starting from the pre-treatment period. It has been observed that the toxicity staging scales commonly used by RT and medical oncology clinics may not match the evaluation criteria of otolaryngology clinics that treat these ear-related side effects.

Notably, the relationship between voice and hearing characteristics of the subjects was complex. While some correlations were observed between certain acoustic parameters and hearing thresholds, particularly in the NPC group, a consistent pattern across all parameters was not evident.

Voice disorders are a common complaint seen at a rate of 30% throughout life. HL is also seen in around 20% of the general population. Although it is suggested that HL may be involved in the pathophysiology of voice disorders, there is insufficient data on this subject.[24] It was found that auditory timbre discrimination and high timbre accuracy in professional vocalists confirm the relationship between hearing and voice quality.[25] In a recent study, it was reported that women with voice disorders have impairments in auditory processing, which determines their ability to distinguish voice patterns associated with the timbre of the voice.[26]

These findings suggest that the mechanisms underlying voice and hearing changes in NPC patients may be multifaceted and may not necessarily be directly linked. It is plausible that both voice and hearing impairments are primarily driven by the effects of radiation therapy on the vocal and auditory systems, respectively.

This study has several limitations. A key limitation of this study is its retrospective design with cross-sectional outcome assessment. While this approach provides valuable data on the prevalence of long-term voice and HL among survivors, its reliance on single post-treatment measurements inherently precludes observation of the temporal course or progression of these functional changes. Consequently, we cannot definitively establish a cause-and-effect relationship between specific therapeutic factors and the measured outcomes. Furthermore, including only patients who maintained adherence to long-term follow-up may have introduced selection bias, potentially underestimating true morbidity rates in the broader NPC survivor population. A similar limitation stems from the heterogeneity of the study population in terms of both NPC disease staging and treatment modalities. Due to the small number of participants in certain stages and treatment subgroups (such as those receiving RT alone or adjuvant CRT), we were unable to statistically analyze voice and hearing outcomes separately by stage or treatment type. Consequently, our findings represent the aggregate outcome of a diverse group of long-term survivors, which may obscure specific correlations between disease severity or specific treatment combinations and observed functional deficits. Second, the perceptual voice assessment was conducted by a single evaluator, which may introduce subjective bias. Third, the

study did not include stroboscopic or aerodynamic voice assessments, which could have provided further insights into vocal fold function. Finally, information on the specific RT techniques and doses received by the patients was limited. The strengths of this study include the relatively large sample size, the evaluation of late-term side effects, the inclusion of both subjective and objective voice assessments, and the comprehensive evaluation of hearing function. This study's comprehensive assessment of both voice and hearing outcomes in NPC survivors fills a gap in the existing literature.

Conclusion

This study demonstrates that NPC patients who undergo RT may experience significant long-term voice and hearing impairments. While the exact mechanisms underlying these impairments remain to be fully elucidated, the findings highlight the importance of routine voice and hearing assessments in the long-term follow-up of NPC patients. Early identification of these impairments can facilitate timely intervention and improve the quality of life for these individuals. Future prospective studies with larger sample sizes and detailed information on treatment modalities are warranted to further investigate the long-term effects of RT on voice and hearing in NPC patients.

Ethics Committee Approval: The Ankara Yıldırım Beyazıt University Ethics Committee granted approval for this study (date: 21.11.2018, number: 12).

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