Volume 20, No 2 | International Journal of Radiation Research, April 2022

The effects of (chemo) radiation therapy on the voice and quality of life in patients with non-laryngeal head and neck cancers: a subjective and objective assessment

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► ***Original article***

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Received: January 2021
Final revised: April 2021
Accepted: may 2021

Int. J. Radiat. Res., April 2022; 20(2): 397-402

DOI: 10.52547/ijrr.20.2.21

Keywords: *Radiation therapy, Head and Neck cancers, Chemotherapy, Quality of life.*

ABSTRACT

***Background*:** Factors affecting the patient's voice and Quality of Life (QOL) by means of Persian Voice Handicap Index (VHI) are important in non-laryngeal Head and Neck Cancers (HNCs) following (chemo)radiation therapy. This study aimed to investigate the vocal problems caused by (chemo)radiation therapy among Iranian patients with non-laryngeal HNCs and to evaluate the factors affecting the patient's voice QOL by means of Persian VHI. ***Material and Methods*:** Seventy patients with non-laryngeal Head and Neck Cancers (HNCs) were treated by radiation therapy, and eighty individuals with normal voice were considered. Acoustic analysis and self-assessment with the Persian VHI questionnaire were performed before, during, and 6 months after the treatment. Normal subjects were tested once. Changes in the acoustic parameters and VHI questionnaire scores over the time and their correlation was assessed using statistical analysis. The effect of important factors on the patient's voice and QOL in different groups was investigated. ***Results*:** The results showed that the acoustic parameters except mean F0, and questionnaire data deteriorated significantly ($P < 0.001$) during the treatment and improved at the final assessment, but not to the initial level. There was a significant relationship between some of the acoustic parameters and subgroups of the VHI questionnaire at the end and 6 months after treatment. Chemotherapy, mean laryngeal dose and smoking were factors that affecting the patient's QOL. ***Conclusions*:** Radiation dose in non-laryngeal tumor in HNCs causes laryngeal damage and vocal problems. Acoustic analysis and Persian VHI questionnaire were two valuable methods in evaluating the patients' voice and QOL. Radiation dose, chemotherapy and smoking greatly impact the aggravation of vocal problems.

INTRODUCTION

At present, (chemo) radiation therapy is one of the most common treatments for Head and Neck Cancers (HNCs) [1]. In patients with non-laryngeal tumors in the head and neck, speech and voice are affected by the radiation treatment. In non-laryngeal cancers, the larynx may be located in the wide fields of radiation and receives high doses [2]. Radiation therapy can damage the larynx, causing voice impairment. The radiation-induced dryness in the pharyngeal region alters the biomechanical properties of the vocal cords and the characteristics of the voice signals [3].

Several objective and subjective methods are used for evaluating the quantity and quality of the voice [4]. Acoustic analysis is a non-invasive and valuable method in diagnosing voice disorders [5,6]. Jitter, shimmer (frequency and amplitude perturbation, respectively), fundamental frequency (F0), and Harmonic to Noise Ratio (HNR) are voice parameters used to distinguish pathological voice signals from those of normal. Jitter and shimmer are valuable predictors of voice pathology [6-9].

Some of the vocal problems are only perceived by the patients and cannot be evaluated by instrumental methods; thus, it is essential to use the questionnaire as a perceptual analysis tool to assess the effects of vocal problems on the patients' Quality of Life (QOL) [1, 10, 11]. In many studies, Voice Handicap Index (VHI) questionnaire was used to assess the patient's QOL [12-17].

There was a measurable and relatively good relationship between the VHI questionnaire and acoustic analysis data in patients with different types of voice disorders [13,14].

[DOI: 10.52547/ijrr.20.2.21]

However, in several studies, vocal problems arising from the radiation treatment for non-laryngeal tumors in HNC have been evaluated, and the results have been reported [3,7,18].

There are some differences between the Persian and English vowel systems [19]; thus, it is necessary to study Persian subjects to compare their results with those of English subjects. This is the first study evaluating Iranian patients' voices with non-laryngeal cancers treated with radiation therapy, using non-invasive methods. This study aims to investigate the effects of the vocal problems caused by radiation therapy on QOL in Iranian patients with non-laryngeal HNCs.

MATERIAL AND METHODS

Subjects

This prospective study was conducted between December 2018 and September 2020, in accordance with medical ethics guideline and criteria approved by Isfahan University of Medical Sciences (IR.MUI.MED.REC.1398.041). Seventy-five patients with normal larynx and non-laryngeal tumors in head and neck were considered who were treated with (chemo) radiation therapy at the Hafte Tir Hospital, Tehran, Iran.

The eligible criteria for individual patient were the larynx had to be uninvolved, the larynx had to been in radiation field, patients' voices should be normal, and all patients were followed at least once.

Five patients due the death and lack of follow-up data were excluded. Seventy patients (46 males, 24 females) remained until the final evaluation. Patient's details and demographic characteristics are shown in table1. Eighty normal individuals who were adjusted with the patients in terms of age, gender, and smoking, and with no history of laryngeal disease participated as a control group. At first, all individuals received a consent form to participate in the test and all steps were explained to them.

Table 1. Demographic, clinical, and treatment characteristics of the patients.

Characteristic	N (%)	Mean	Median (Range)
Gender			
Male	46 (65)		
Female	24 (35)	-	-
Age	-	50.50	50.43 (14-82)
Delivered Dose (Gy)	-	50.53	60 (46-70)
Tumor site			
Nasopharynx	24 (34)		
Oral Cavity	15 (21.5)		
Neck Lanphoma	18 (26)	-	-
Parotid	13 (18.5)		
RT modality	(3D-CRT)		
concurrent chemotherapy			
No	27 (39)	-	-
Yes	43 (61)		

Chemo-radiation treatment and Laryngeal dose

All patients underwent Computed Tomography (CT, Siemens, Germany) simulation before (chemo) radiation therapy.

They were treated using 3D-Conformal Radiation Therapy (3D- CRT) modality and Treatment Planning System (TPS), the CorePlan (version 3.5.0.5, Seoul C&J Co., Seoul, South Korea), based on the patient CT scans. For treatment planning tumor tissue as target and larynx as OAR were contoured on CT slices. Depending on the type of tumors and the prescribed doses all patients underwent about 23 to 35 courses with total doses of 46 to 70 Gy and dose per fraction of 1.8 or 2 Gy, in 5 consecutive days per week.

After dose calculations, larynx differential Dose Volume Histograms (dDVHs) were calculated and the mean laryngeal dose was determined.

Out of seventy patients, 43 patients (28 males, 15 females) underwent concurrent chemo-radiation therapy with receiving (40 mg/m2) Cisplatin (Bristol Myers Squibb, United *States*) once a week.

Voice assessment

Acoustic analysis

In order to record patients' voice, in a completely quiet room, each patient sat comfortably on a chair with a microphone at the distance of 7 cm from his/her mouth. A Recorder Stereo Microphones (H5, Zoom, Japan) was used to record the voice samples. The voice recording was made at the sampling frequency of 44.1 kHz with 16 bit per sample. The patients were asked to sustain the vowel / a / for 5 seconds in the habitual loudness. The recorded voices were transferred to a computer in wave format and three seconds of each samples were selected and acoustic parameters were extracted. PRAAT software (version, 6.0.25) was used for acoustic analysis.

All patients completed Persian VHI questionnaire. This questionnaire had 30 questions in three subgroups include physical, emotional, and functional aspects. Each of them contains 10 questions. Patients filled in the VHI questionnaire and the options they chose were scored as follows: 0 = never, 1= almost never, 2 = sometimes, 3 = almost always and 4 = always. The total score of the questionnaire was 120 [15, 17]. The Persian version of the VHI questionnaire with a Cronbach's alpha of 0.87 showed that it is a suitable tool for assessing the QOL in patients with the vocal problems [14, 20, 21]. For this questionnaire the total score of 14.5 or higher considered as abnormal [22]. All tests were repeated in three time points, before, end, and six months after treatment except for the control group which was performed once. Control group data were compared with the pre-treatment results for patients and were considered as a criterion admission.

All voice samples were analyzed using PRAAT software. Several acoustic parameters including mean fundamental frequency (F0), HNR, types of

[DOI: 10.52547/ijrr.20.2.21]

jitter: local, Relative Average Perturbation (RAP), Difference of Differences of Period (DDP), types of shimmer: Local in dB, three-point Amplitude Perturbation Quotient (APQ3), and Difference of Differences of Amplitude (DDA) were selected and analyzed.

In order to evaluate the effect of various factors such as chemotherapy, mean laryngeal dose, smoking, age and gender on the patients' voice and QOL. Then, the patients were divided into several groups, male and female with age >50 years and age <50 years, smoker and non-smoker, mean laryngeal dose of greater and smaller than 44 Gy and having chemo-radiotherapy or radiotherapy alone.

Statistical analyses

Kolmogorov-Smirnov test used to assess the normality of all Persian VHI questionnaires and the acoustic data. Using descriptive statistics calculated the median and Interquartile Range (IQR) for all data. Friedman test was used to examine the changes in all data over the time. Spearman's correlations were applied to assess relationships among acoustic parameters and questionnaire data in assessment points. Mann-Whitney test was taken to assess the differences between questionnaire score in different groups. Statistical analyses were performed using the software SPSS (version, 22.0) and Significance level P¬4.49 was considered.

RESULTS

The Kolmogorov-Smirnov test results showed that the acoustic analysis data and the VHI questionnaire scores did not have a normal distribution in the three mentioned time points. For this reason, the non-parametric Friedman test was used.

Friedman test revealed that the median and IQR for all acoustic parameters except F0 for male (P = 0.316) and female (P=0.214), significantly changed over the time (P<0.001). Acoustic parameters of the voice samples (29/70) 41.42% increased during the treatment and decreased 6 months after it, but did not reach to the pre-treatment values. This trend was reversed for HNR (P<0.001), (table 2). All Persian VHI questionnaires and acoustic analysis data were evaluated at three time points.

The results of the VHI questionnaire evaluation (42/70) 57.14% patients showed that the score of all subgroups of the VHI questionnaire increased during the treatment, and then decreased (figure 1).

Spearman correlation showed that no significant relationship was found between any of acoustic analysis data and scores of VHI questionnaire subgroups before treatment. At the end of treatment, there was an important relationship between physical subgroup and DDA (%) (r=0.280, P=0.045), functional subgroup, APQ3(%) (r=0.112, P=0.041) and, DDP (%) (r=0.320, P=0.001), and between total group with DDP (%) (r=0.292, P=0.035). At 6 months after treatment, there was a significant relationship inversely between of physical subgroup and APQ3 (%) (r=-0.301, P=0.048), functional subgroup and total with HNR (r=-0.299, P=0.022, r=-0.294, P= 0.025), and emotional subgroup and the local jitter (%) (r=-0.263, P= 0.028) (table 3).

Using Mann-Whitney test, the effect of various factors on the voice was investigated. Results of evaluating the VHI questionnaire in the final assessment in three subgroups revealed that concurrent (chemo) radiation therapy (P=0.037) higher laryngeal mean (P=0.045) dose and history of smoking (P=0.001) had significant effect on reducing the quality of voice. Consequently, the patient's QOL and changes in age (P= 0.077) and gender (P=0.103) were not significant (figure 2).

Table 2. Median and Interquartile Range (IQR) of Acoustic parameters analysis in three times for patients and control group.

Time / Acoustic parameter	control group	pre of treatment	end of treatment	6 months after of treatment	P-value*
F0 (male)	120.044 [21.634]	119.514 [20.553]	136.524 [24.093]	122.512 [22.893]	0.316
F0 (female)	195.810 [30.012]	199.015 [32.678]	206.144 [58.32]	196.865 [25.138]	0.214
jitter (local)%	0.311 [0.215]	0.365 [0.205]	0.870 [0.439]	0.592 [0.3]	<0.001*
jitter (RAP)%	0.201 [0.114]	0.298 [0.278]	0.723 [0.971]	0.571 [0.426]	<0.001*
jitter (DDP)%	0.305 [0.201]	0.315 [0.208]	0.922 [0.227]	0.568 [0.268]	<0.001*
shimmer (local dB)	0.423 [0.292]	0.440 [0.317]	0.861 [1.296]	0.613 [0.528]	<0.001*
shimmer (APQ3)%	2.89 [2.761]	3.439 [2.913]	5.710 [5.307]	4.075 [4.015]	<0.001*
shimmer (DDA)%	1.361 [0.423]	1.459 [0.601]	2.633 [1.092]	1.716 [0.63]	<0.001*
HNR	21.015 [5.98]	22.417 [5.014]	18.616 [5.961]	21.159 [6.59]	<0.001*

*Significant difference in P<0.05, Result from statistical analysis and Friedman Test, Relative Average Perturbation (RAP), Difference of Differences of Period (DDP), three-point Amplitude Perturbation Quotient (APQ3), Difference of Differences of Amplitude (DDA)

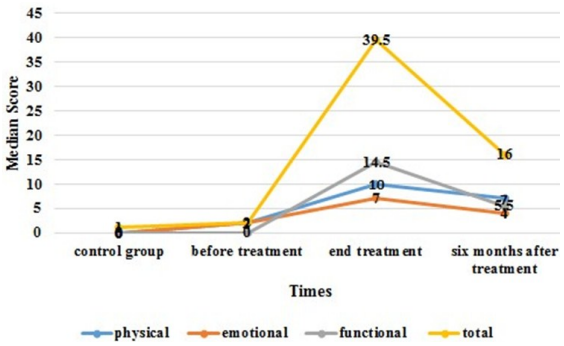

Figure 1. Changes of the three subgroups score of the Persian VHI questionnaire and the control group at the evaluation times.

[DOI: 10.52547/ijrr.20.2.21]

Table 3. Correlation between of Acoustic parameters and VHI questionnaire subgroups in three times.

Times	acoustic parameters	types of jitter & shimmer	physical	functional	emotional	total
before of treatment	jitter	Local (%)	0.034	0.199	0.095	0.120
		RAP (%)	-0.036	-0.30	0.002	0.009
		DDP (%)	-0.060	0.034	0.175	0.042
	shimmer	local (dB)	-0.055	0.009	0.113	0.001
		APQ3 (%)	-0.214	-0.096	-0.023	-0.109
		DDA (%)	-0.055	0.089	0.189	0.074
	HNR	-	0.0.59	0.0.29	-0.91	0.012
	mean F0	-	-0.254	-0.188	-0.220	-0.218
end of treatment	jitter	Local (%)	-0.121	-0.109	0.057	-0.111
		RAP (%)	0.099	0.171	0.184	0.154
		DDP (%)	0.174	0.320**	0.186	0.292*
	shimmer	local (dB)	0.188	0.145	-0.208	0.137
		APQ3 (%)	0.161	0.112*	0.115	0.168
		DDA (%)	0.280*	0.139	0.198	0.214
	HNR	-	-0.165	-0.066	-0.83	-0.092
	mean F0	-	0.195	0.095	0.210	0.108
six months after of treatment	jitter	Local (%)	-0.082	0.051	-0.263*	-0.119
		RAP (%)	0.061	-0.036	0.029	0.022
		DDP (%)	0.060	-0.019	-0.170	-0.031
	shimmer	Local (dB)	0.220	0.125	0.082	0.155
		APQ3 (%)	-0.301*	-0.142	-0.026	-0.208
		DDA (%)	-0.146	-0.128	0.185	-0.164
	HNR	-	-0.225	-0.299*	-0.108	-0.294*
	mean F0	-	-0.118	0.039	-0.159	-0.156

Results for spearman correlation between Acoustic parameters and VHI subgroup questionnaire. Relative Average Perturbation (RAP), Difference of Differences of Period (DDP), three-point Amplitude Perturbation Quotient (APQ3), Difference of Differences of Amplitude (DDA). *Correlation is significant at the 0.05 level (2-tailed). ** Correlation is significant at the 0.01 level (2-tailed).

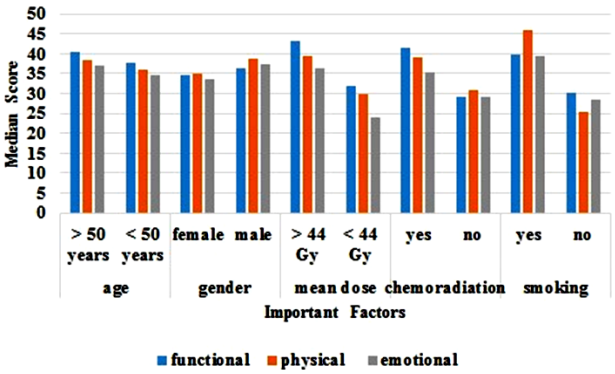

Figure 2. Evaluation of the effect of important factors on the voice and patient's QOL based on the Persian VHI questionnaire subgroup scores. The laryngeal mean dose, chemotherapy and smoking are important factors that affect the voice.

DISCUSSION

Out of all studied patients (39/70), 55.71 % received the mean dose of higher than 44 Gy in the larynx; this dose causes grade II or higher edema in the larynx [23]. Patients who received a mean dose of higher than 44 Gy and had higher Persian VHI questionnaire scores in the 6 months after treatment reported voice change and deterioration compared to before treatment. They complained of voice problems, thus reducing social communication.

The edema and resulting fibrosis change the vibrational pattern of the vocal cords, possibly leading to long-term vocal problems [11]. Changes in the voice and acoustic signal characteristics are related to the dose to the larynx and oral cavity [24].

Although acoustic analysis and self-assessment, using the VHI questionnaire, are two different methods in assessing voice and laryngeal damage, a relationship between them has been confirmed in various studies [13,14]. Before treatment, due to the presence of normal signals, the values of the disturbance parameters (jitter and shimmer) were very small, and there was no correlation between the values of the acoustic parameters and the scores of the VHI questionnaire.

At the end of treatment, there was a significant and direct relationship between values of jitter and shimmer with the score of functional subgroup, shimmer with physical subgroup, and jitter with the total score. Voice problems and their effect on patients' QOL increase the rate of vocal disability, questionnaire scores, and disturbance of acoustic signals [13]. This can explain the strong and positive correlation between the values of the subgroups and the acoustic parameters at the end of treatment. Longer follow-ups (up to 8 years) have shown the values of acoustic parameters to be closer to pre-treatment levels; however, in self-assessment, patients still complain of vocal problems [25]. In the final evaluation, an inverse relationship between some values of acoustic parameters and subgroups (jitter with emotional, shimmer with physical, and HNR with functional subgroups) also confirms the presence of voice problems perceived by the patient.

Niebudek *et al.* (2010) [13] found a positive relationship between acoustic parameters and subgroups of the VHI questionnaire due to the subjects' uniformity; while in this study, the subjects had different cancers and mean doses in the larynx.

[DOI: 10.52547/ijrr.20.2.21]

The differences in some of the results were due to differences in the disease of the experimental groups, the vowel system and the threshold value for the VHI questionnaire in different languages, voice problems, and emotional states and awareness level of patients.

The results of acoustic analysis and the scores of the VHI questionnaire in similarity and conformity with those of other studies performed in English subjects confirm the ability of acoustic analysis and Persian VHI questionnaire in assessing voice problems and laryngeal damage in Iranian subjects [14, 21, 22].

In another evaluation, the effect of various factors, such as age, gender, smoking, chemotherapy, and the laryngeal mean dose, was assessed on patients' QOL. Under the same conditions, patients with different genders and age groups presented similar results concerning voice quality and the treatment impact on their QOL.

3D-conformal radiation therapy with the wide fields of radiation affects the large volume of the OARs [4].

Exposure of a large volume of the larynx in the treatment field increases the dose, thus the mean dose. People with doses higher than 44 Gy have many voice problems. Concurrent (chemo) radiation therapy at least doubles the incidence of vocal problems to radiation therapy only [18]. Chemotherapy, smoking, and extra radiation dose are important factors in increasing vocal problems [26, 27].

The scores of VHI questionnaire subgroups increased in smokers who underwent chemotherapy and had a high mean laryngeal dose. In this study, all patients were treated with the 3D-CRT modality. Intensity modulation radiation therapy (IMRT) and Image-Guided Radio Therapy (IGRT) can reduce the dose to the larynx, thus reducing edema and fibrosis, and consequently, voice problems [28].

The positive points of the present study include considering two evaluation methods, objective and subjective; having a control group for accurate patient admission; examining the effect of influential factors on the patient's voice; using baseline data. All of these factors are necessary for a comprehensive investigation. This is the first work evaluating the qualitative aspects of vocal problems using the Persian VHI questionnaire in Iranian patients with non-laryngeal tumor HNCs. Determination of factors affecting the voice can make it possible to reduce the negative effects on the patients' QOL with the help of rehabilitation specialists.

CONCLUSION

(Chemo) radiation therapy in patients with non-laryngeal tumor HNCs can damage the larynx, thus causing vocal problems. Acoustic analysis and patient self-assessment are the best assessment methods due to their cheapness, non-invasiveness, and high repeatability. In addition to radiation dose, chemotherapy and smoking greatly impact the aggravation of vocal problems.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the staff of radiation therapy Department at the Hafte Tir Hospital, Tehran, Iran. for their good cooperation.

Conflict of interest: The authors declare that they have no conflicts of interest.

***Ethical approval*:** This work was done according to Ethical code no: IR.MUI. MED.REC.1398.041.

***Funding*:** This work is a part of PhD thesis which is financially supported (grant no: 397780 with ethical code no: IR.MUI.MED.REC.1398.041) by the Isfahan University of Medical Sciences, Isfahan, Iran.

***Author contribution*: S B,** contributed in the conception of the work, contributed in the writing, and agreed for all aspects of the work. **D SG,** contributed in the conception of the work, conducting the study, contributed in the writing, editing and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. **F T,** contributed and conducting the study, and agreed for all aspects of the work. **SR M,** contributed and conducting the study, and agreed for all aspects of the work. **S S,** contributed and conducting the study, and agreed for all aspects of the work.

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[DOI: 10.52547/ijrr.20.2.21]