Original Article

Binary Logistic Regression Modeling of Voice Impairment and Voice Assessment in Iranian Patients with Nonlaryngeal Head-and-Neck Cancers after Chemoradiation Therapy: Objective and Subjective Voice Evaluation

Abstract

Background: Laryngeal damages after chemoradiation therapy (RT) in nonlaryngeal head-and-neck cancers (HNCs) can cause voice disorders and finally reduce the patient's quality of life (QOL). The aim of this study was to evaluate voice and predict laryngeal damages using statistical binary logistic regression (BLR) models in patients with nonlaryngeal HNCs. **Methods:** This cross-section experimental study was performed on seventy patients (46 males, 24 females) with an average age of 50.43 ± 16.54 years, with nonlaryngeal HNCs and eighty individuals with assumed normal voices. Subjective and objective voice assessment was carried out in three stages including before, at the end, and 6 months after treatment. Eventually, the Enter method of the BLR was used to measure the odds ratio of independent variables. **Results:** In objective evaluation, the acoustic parameters except for F0 increased significantly ($P < 0.001$) at the end treatment stage and decreased 6 months after treatment. The same trend can be seen in the subjective evaluations, whereas none of the values returned to pretreatment levels. Statistical models of BLR showed that chemotherapy ($P < 0.05$), mean laryngeal dose ($P < 0.05$), V50 Gy ($P = 0.002$), and gender ($P = 0.008$) had the greatest effect on incidence laryngeal damages. The model based on acoustic analysis had the highest percentage accuracy of 84.3%, sensitivity of 87.2%, and the area under the curve of 0.927. **Conclusions:** Voice evaluation and the use of BLR models to determine important factors were the optimum methods to reduce laryngeal damages and maintain the patient's QOL.

Keywords: *Head-and-neck neoplasms, laryngeal diseases, logistic models, radiotherapy, voice disorders*

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Introduction

Head-and-neck cancers (HNCs) are a group of cancers that involve several anatomical sites in the head-and-neck area.[1] Radiation therapy (RT) is a major method in the treatment of HNCs that can be prescribed with or without chemotherapy.[2] One of the problems of RT is to reach the damage to healthy organs near the tumor.[3] In most HNCs, the normal larynx is located in radiation fields due to its placement in the neck area and receiving high radiation doses.[4] Since the voice originates from the larynx, any vocal problems are a sign of laryngeal damages and dysfunction of the vocal cords. The voice is a multidimensional phenomenon and all quantitative and qualitative aspects of vocal problems should be evaluated.[3] Acoustical analysis of voice signals,[4,5] self-assessment by questionnaires,[6-8] and perceptual assessment are well-known methods of voice examination.[9,10] Several studies have used either of these methods to evaluate vocal problems.[10-14] However, this is the first study that was performed for Persian speakers. As the vowel system is different in English and Persia,[15] it was necessary to evaluate vocal problems and laryngeal edema in Iranian patients with nonlaryngeal HNCs.

Laryngeal damages and vocal problems are among the most important complications to be understood from chemo-RT for HNCs.[16] One of the important issues in the group of heterogeneous patients with different HNCs is the difference in the type

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of cancer, the type of treatment (chemoradiation or only radiation), different values of dosimetric parameters, and the individual conditions of each patient such as age and gender. As a result, it can mean that there is a different likelihood of complication or outcome for each patient.

Considering the mentioned conditions, the two issues of the effect of each factor in incidence complication as well as the difference or similarity in the results of each evaluation approach need further investigation.

Identifying factors that influence damages plays an effective role in disease prevention.[17] The use of appropriate statistical models and accurate estimation methods in conjunction with clinical diagnostics can be effective in determining these factors appropriately.[18,19] Binary logistic regression (BLR) is a statistical technique to analyze the relation of a dependent variable to one or more independent variables in the research plans.[20-24] In none of the previous studies so far, the results of different evaluation methods and the effect of each factor in the incidence of laryngeal damages have not been investigated. Accordingly, the aim of the present study was to assess vocal changes and laryngeal dysfunction, especially laryngeal edema through objective and subjective evaluation of voice, as well as develop statistical models to improve disease detection by investigating effective factors in laryngeal dysfunction. For this purpose, BLR models were used to compare the performance of each of the assessment methods in classifying patients in the damaged and normal groups.

Materials and Methods

Seventy patients including 46 (65.71%) males and 24 (34.28%) females with a mean age of 50.43 ± 16.54 years, with various nonlaryngeal HNCs, were recorded in this cross-section experimental study. Descriptive analysis and related details about the types of malignancy and patient's conditions are given in Table 1. This experimental study was conducted in Haft Tir Hospital (Tehran, Iran) between December 2018 and September 2020. The present study was conducted following the approval of the Ethical Committee of Isfahan University of Medical Sciences (Isfahan, Iran, with ethical code number of IR. MUI. MED. REC.1398.041). All patients and the control group signed the consent form. The criteria for the patient's admission include no history of laryngeal disease and having a normal voice.

Chemoradiation therapy and dosimetry

Three-dimensional conformal RT (3D-CRT) was performed using a Siemens PRIMUS medical linear accelerator (Siemens AG, Erlangen, Germany) with MV energy located in Haft Tir, RT center. Before starting treatment, all patients were immobilized in the supine position for computed tomography (CT) simulation (Siemens Healthcare, Forchheim, Germany) and a four-point mask was used for each patient to repeat the position during treatment. CT images were obtained with 3-mm slice thickness. The CT images were converted into the Digital Imaging and Communications in Medicine format and transferred to the ISOgray treatment planning system (TPS) (DOSIsoft, French). The gross tumor volume, clinical target volume, and planning target volume as well as larynx as an organ at risk (OAR) were contoured on each slice of the CT images.[25] The doses of RT depending on the type of tumor ranged from 46 to 70 Gy for neck lymphoma and nasopharynx cases, respectively. All patients were treated five times a week, consecutively at a dose of fraction 1.8–2 Gy per day. In addition to RT, a number of patients (28 males, 15 females) had cisplatin-based chemotherapy, once a week. In order to calculate the mean, minimum, and maximum doses and V50 Gy in 27% of the larynx volume, a dose–volume histogram (DVH) was extracted from the TPS.

Table 1: Descriptive statistics for the general characteristics of studied subjects

Characteristic	*n* (%)	Mean
Gender		
Male	46 (65.71)	-
Female	24 (35.28)	
Age	-	50.50
Smoker	38 (54.28)	-
Male	34 (48.57)	
Female	4 (5.71)	
Nonsmoker	32 (45.71)	
Delivered dose (Gy)	-	50.53
Tumor site		
Nasopharynx	24 (34)	-
Oral cavity	15 (21.5)	
Neck lymphoma	18 (26)	
Parotid	13 (18.5)	
RT modality		
Concurrent chemotherapy	3D-CRT	-
No	27 (39)	
Yes	43 (61)	

RT – Radiation therapy

Voice evaluation

Three methods of voice evaluation including acoustic analysis, self-assessment use of Persian Voice Handicap Index (VHI) questionnaire, and perceptual evaluation were used to diagnose voice disorders and laryngeal damages in patients with nonlaryngeal HNCs. Data from eighty normal individuals were obtained as a control group. The eligible criteria for the individual patient were the larynx had to be uninvolved, the larynx had been in the radiation field, patients' voices should be normal, and all patients were followed at least once. People should not have any difficulty swallowing. In all evaluation methods, if the pretreatment data for patients were in line with the aforementioned control group's data, patients were entered in the relevant experiments.

Objective assessment

In a quiet room, the voices of all patients were recorded. All patients sustained the vowel/a/twice in the most habitual situations for 5 s, then counted the numbers from 1 to 10, and read the standard text "Pedarbozorg." This text was developed to assess voice samples in Iranian patients with vocal dysfunctions.[26] The participants were instructed to produce an/a:/as long as possible after taking a maximal inhalation at a comfortable pitch and at their habitual loudness. Maximum phonation time (MPT) was expressed in seconds.

The recordings were conducted with a sampling frequency of 44.1 kHz and transferred to the computer system. Three seconds of vowel/a/and the whole time of other recorded voices were selected and analyzed using PRAAT software (version, 6.0.25) (Boersma,& Weenink, 2015) software (Finger,Cielo, Schwarz, 2015). The voices were recorded with the Zoom (H5, Japan) recorder.[27]

Subjective assessment

Patients were given a Persian version of the VHI questionnaire. This questionnaire has 30 questions in three subgroups; emotional, functional, and physical. Each subgroup has 10 questions and each question is rated from 0 to 4 scores. The total score of the questionnaire is 120. In the Persian VHI questionnaire, the cutoff point for the presence of voice impairments is 14.5.[28]

Perceptual evaluation

All patients read the standard text of the "Pedarbozorg," again inconsistent conditions. Perceptual evaluation of vocal disorders was performed using of GRBAS scale. This scale consisted of G (grade), R (rough), B (breathy), A (asthenia), and S (straining). The mean overall voice severity parameter "G," from the GRBAS ranged from G = 0–3 (0 = normal, 1 = mild, 2 = moderate, and 3 = severe) considered for each patient.[27] Two experienced speech therapists, completely unaware of the patient's condition evaluated any voice samples separately. All the mentioned tests were repeated in three times points including before, end, and 6 months after treatment. Sustaining the vowel was used for acoustic analysis of voice signals, numbers were counted to obtain habitual frequency, and "Pedarbozorg" text was used for perceptual evaluation. A total of 840 sound samples were obtained from patients and 240 samples from the control group.

Data analysis methodology

Binary logistic regression model

Logistic regression (LR) was introduced in the late 1960s and became popular among all researchers, especially health researchers.

Regression analysis presents the association between an outcome (dependent) variable and one or more predicted (independent) variables. BLR is used when the outcome variable had two categories.[22,27] In this study, laryngeal damages were considered as dependent variables (presence = 1, absent = 0) and chemotherapy, mean, maximum, and minimum doses in the larynx, V50 Gy in the volume of 27% or higher of the larynx, smoking status, age, and gender were considered as independent variables. At the first, the collinearity statistical test was carried out to investigate the collinearity between the predictor variables. For all predictor variables, there were no collinearity trends, (tolerance >0.4).

For all voice evaluation methods, univariate and multivariate BLR models were computed. In the univariate analysis, the results from the LR and the Pearson Chi-square test were calculated and compared.

Variables with ($P < 0.1$) in the univariate analysis were entered into the multivariate analysis. The Enter method of BLR was used to measure the odds ratio (OR) of each variable in this research at the *P* level.

The results for three BLR models were evaluated in terms of performance with receiver operating characteristics curve and the area under the curve. One of the best ways to validate the damage was to perform a laryngoscopy, but this was avoided due to the damage caused by the RT and the problems for the patients.

Statistical analysis

The normality of all data was evaluated with the Kolmogorov–Smirnov test. The data for the control group and patients before treatment presented a normal distribution ($P > 0.05$). Independent samples *t*-test was used to compare the mean values between one standard deviation (mean ± SD) of acoustic parameters and questionnaire subgroups scores in two groups. Due to the abnormal distribution ($P < 0.05$) of patient's data at three times points (before, end, and 6 months after treatment), the nonparametric Friedman test was used to compare over time. All analyses were performed with the use of SPSS software (IBM Crop. 2019. IBM SPSS, version 26.0, IBM Corp., Armonk, N.Y., USA), and the significance level of $P < 0.05$ was considered in this study.

Results

The values of important acoustic parameters including jitter (%) and shimmer (%) (period-to-period irregularities in frequency and in amplitude), respectively, main fundamental frequency (F0), habitual frequency pitch, harmonic-to-noise ratio (HNR), and noise-to-harmonic ratio (NHR) were extracted using of PRAAT software. The results of the independent samples *t*-test related to objective and subjective evaluations for the control group and patients before treatment are shown in Table 2. There was no significant difference ($P > 0.05$) in the mean ± SD values between the two groups in both evaluation methods. In contrast, the results of the Friedman test for acoustic analysis in the patient's group are shown in Figure 1, Part A. Results show significant changes in the mean ranks for all acoustic parameters ($P < 0.001$), except main fundamental frequency (male $P = 0.316$, female $P = 0.214$), frequency range (male $P = 0.221$, female $P = 0.311$), and MPT (male $P = 0.411$, female $P = 0.219$). Acoustic parameters increased during the treatment and decreased 6 months after treatment. Changes for HNR were in the opposite direction of the mentioned parameters. The results of the Persian VHI questionnaire and the perceptual assessment are given in Sections B and C of Figure 1. For the Persian VHI questionnaire, the mean rank of the values in all three subgroups and the total group increased significantly ($P < 0.001$) during the treatment and decreased in 6 months after treatment but did not reach the base level. Interrater agreement for GRBAS rating between two experienced experts was measured using the intraclass correlation coefficient, and the excellent result was (0.921). Perceptual evaluation of voice quality was measured by GRBAS grade. Friedman test results and frequency show

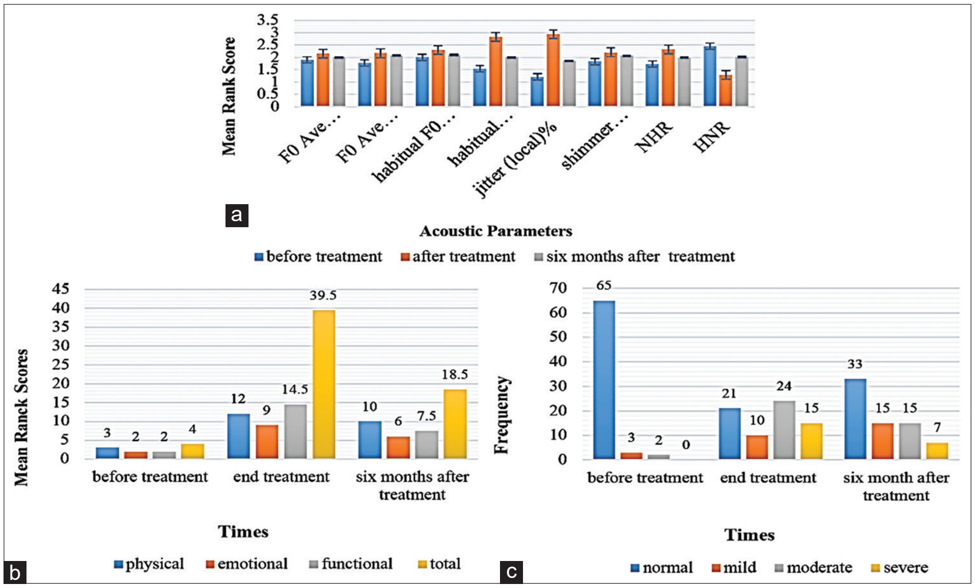

Figure 1: Voice assessment based on; (a) Acoustic analysis in patients group at three times (before treatment, after treatment, and 6 months after treatment); (b) Persian VHI questionnaire in physical, emotional, functional subgroup and total at the over time; (c) GRBAS (G: Grade, R: Rough, B: Breathy, A: Asthenia, and S: Straining) scale in patients group in three evaluation times: (before, end, and 6 months after treatment). Abbreviation: HNR – Harmonic-to-noise ratio; NHR – Noise-to-harmonic ratio

Table 2: Mean±standard deviation of acoustic parameters for control group and patients in before treatment

Voice evaluation	Parameters	Control Group	Patients group before treatment	*t*	*P*
Acoustic Analysis	F0 average (male) (Hz)	120.14±14.632	117.074±10.471	1.145	0.256
	F0 range (male) Hz	(98.14-173.08) ±14.63	(98.66-153.11) ±10.47	0.917	0.363
	F0 Ave (female) Hz	191.353±27.543	197.254±18.958	0.810	0.420
	F0 range (female) Hz	(165.40-248.49) ±27.54	(173.37-253.51) ±18.95	1.261	0.212
	Mean Habitual pitch (male) Hz	131.107±15.386	128.447±15.561	0.423	0.673
	Mean Habitual pitch (female) Hz	186.204±17.047	191.358±12.984	1.637	0.104
	Jitter (local) %	0.397±0.151	0.407±0.156	1.422	0.167
	Shimmer (local)%	3.876±2.069	3.322±2.065	1.021	0.309
	HNR	21.439±2.512	22.157±3.628	1.323	0.201
	NHR	0.018±0.011	0.015±0.01	1.441	0.311
	MPT (male) sec	25.12±5.3	23.14±8.2		
	MPT (female) sec	18.15±3.01	19.54±6.11		
GRBAS	Grade	0.314±0.305	0.341±0.293	0.392	0.553
VHI questionnaire subgroups	Physical	0.512±0.129	0.557±0.137	1.066	0.288
	functional	0.375±0.163	0.428±0.112	1.275	0.204
	emotional	0.387±164	0.471±146	1.315	0.191
	Total	1.625±1.325	1.988±1.561	0.859	0.392

*Significant difference in $P<0.05$, Result from independent samples *t*-test. HNR – Harmonic-to-noise ratio; NHR – Noise-to-harmonic ratio; MPT – Maximum phonation time; VHI – Voice Handicap Index; GRBAS – Grade, rough, breathy, asthenia, and straining significant changes ($P < 0.001$) between each of grade values at any given time.

Binary logistic regression models

Acoustic analysis

According to the acoustic analysis 6 months after treatment, 31 (44.28%) patients were classified in the damaged group. The results of the univariate analysis using the LR method (likelihood ratio) and the Pearson Chi-square coefficient were virtually the same for all variables. The omnibus tests demonstrated that the resulting model is significant (Chi-square = 48.330, df = 6, $P < 0.001$ and Cos and Snell $R^2 = 0.499$, Nagelkerke $R^2 = 0.668$).

In multivariate analysis, the variables of chemotherapy, mean laryngeal dose, and V50 Gy showed a significant level ($P < 0.05$). The BLR result showed a true classification rate of 87.1%. In other words, the regression model classified 27 out of 31 cases exactly, as expected in Table 3.

Subjective assessment

Persian Voice Handicap Index questionnaire

Based on the cutoff value for vocal problems in the Persian VHI questionnaire, 42 (60%) patients with a score higher than 15 were classified as damaged.

The results of omnibus test for this model such as Chi-square and df were 18.430 and 4, respectively ($P < 0.001$). Independent variables can predict 20%–28% of the variance of laryngeal damage (Cos and Snell $R^2 = 0.209$, Nagelkerke $R^2 = 0.283$). Multivariate analysis showed that chemotherapy and mean laryngeal dose are the important factors with $P < 0.05$. The true classification rate was 83.3%; in other words, the regression model classified 35 out of 42 cases correctly; Table 4.

Perceptual assessment

Based on perceptual evaluation, 37 (52.85%) patients had high G-score >1.5 and were classified in the damaged group. In multivariate analysis, the variables of gender and mean laryngeal dose were the influential variables with a significant level of $P < 0.05$. Results from omnibus tests demonstrated that model is significant (Chi-square = 19.773, df = 4, $P < 0.001$) and can predict 24%–32% of the variance of laryngeal damage (Cos and Snell $R^2 = 0.246$, Nagelkerke $R^2 = 0.328$). The true classification rate was 81.1%, and 29 of the 37 patients were classified correctly [Table 5]. The comparison results of the three models are shown in Table 6. ROC diagrams for each model are also shown in Figure 2.

Discussion

Two tasks were performed in this experimental study: the first the assessment of voice as an important factor in the diagnosis of laryngeal edema and the second predicting the likelihood of damage based on various factors and use of statistical BLR models.

In this study, compared to the control group and pretreatment data, the values of the acoustic parameters increased at the end of treatment. Hoarseness, breathiness, and roughness are common indicators of change in voice signals. In the presence of vocal problems, these signs increase. The increase in values of perturbation parameters (jitter, shimmer, and NHR) indicates hoarseness of the voice. A decrease in HNR indicates the presence of breathiness, and roughness is related to the increased values of the main fundamental frequency and habitual frequency.[27,28]

Table 3: Univariate and multivariate analysis of factors predictive of laryngeal damages used of binary logistic regression model based on acoustic analysis at 6 months after of treatment

Variables	β	OR	95%CI (OR)	*P*	Pearson Chi-square	Likelihood ratio
Age	1	2.718	1.016-7.268	0.046*	4.060	4.117
Gender	0.095	1.100	408-2.967	0.851	0.035	0.035
Smoking	0.896	2.450	0.918-6.538	0.074*	3.262	3.304
Chemotherapy	2.489	12.054	3.498-41.536	<0.001*	18.658	20.211
Mean dose	2.583	13.236	4.050-43.260	<0.001*	22.478	23.019
Maximum dose	2.320	10.175	2.051-50.489	0.005*	10.824	11.091
V50 Gy	2.376	10.767	3.293-35.205	<0.001*	18.009	18.756
Multivariate analysis						
Variables	**β**	**OR**	**95%CI (OR)**	***P***		
Age	−0.085	0.919	0.190-4.452	0.913		
Smoking	1.187	3.276	0.628-17.079	0.159		
Chemotherapy	+1.762	5.823	1.620-53.543	0.031**		
Mean dose	+2.231	9.313	1.335-32.304	0.012**		
Maximum dose	+1.081	2.978	0.388-22.395	0.296		
V50 Gy	+2.660	14.292	2.680-76.205	0.002**		

*Significant at the *P*<0.1 level in univariate analysis, **Significant at the *P* 0.05 level in multivariate analysis. CI – Confidence interval; OR – Odds ratio

Table 4: Univariate and multivariate analysis of factors predictive of laryngeal damages used of binary logistic regression mode; based on Persian Voice Handicap Index questionnaire at 6 months after of treatment

Variable	β	OR	95%CI (OR)	*P*	Pearson Chi-square	Likelihood ratio
Age	0.026	2.167	0.818-5.737	0.120	2.456	2.462
Gender	−0.105	0.900	0.330-2.458	0.837	0.042	0.042
Smoking	0.629	1.875	0.711-4.942	0.204	1.631	1.631
Chemotherapy	1.624	5.073	1.802-14.277	0.002*	10.045	10.172
Mean dose	1.719	5.577	1.954-15.920	0.001*	11.046	11.336
Maximum dose	1.529	4.613	0.937-22.717	0.060*	4.031	4.480
V50 Gy	1.012	2.750	0.924-8.180	0.069*	3.424	3.547
Multivariate analysis						
Variables	**β**	**OR**	**95%CI (OR)**	***P***		
Chemotherapy	1.170	3.221	1.049-9.895	0.041**		
Maximum dose	0.358	1.430	0.228-8.965	0.702		
V50 Gy	0.547	1.728	0.510-5.853	0.380		
Mean dose	1.317	3.732	1.210-11.512	0.022**		

*Significant at the *P*<0.1 level in univariate analysis, **Significant at the *P*<0.05 level in multivariate analysis. CI – Confidence interval; OR – Odds ratio

Table 5: Univariate and multivariate analysis of factors predictive of laryngeal damages used of binary logistic regression model, based on grade, rough, breathy, asthenia, and straining at 6 months after treatment

Variables	β	OR	95%CI (OR)	*P*	Pearson Chi-square	Likelihood ratio
Age	0.010	0.980	0.382-2.515	0.967	0.002	0.002
Gender	1.150	3.157	1.098-9.07	0.033*	4.736	4.853
Smoking	0.090	1.094	0.425-2.813	0.853	0.035	0.035
Chemotherapy	1.043	2.836	1.061-7.581	0.038*	4.427	4.465
Mean dose	1.553	4.727	1.721-12.984	0.003*	9.550	9.769
Maximum dose	0.846	2.330	0.643-8.442	0.198	1.718	1.762
V50 Gy	0.868	2.381	0.852-6.656	0.098*	2.795	2.838
Multivariate analysis						
Variables	**β**	**OR**	**95%CI (OR)**	***P***		
Gender	+1.733	5.656	1.582-20.225	0.008**		
Mean dose	+1.744	5.723	1.531-17.915	0.004**		
v50 Gy	0.556	1.744	0.522-5.831	0.366		
Chemotherapy	+1.420	4.136	0.931-10.225	0.022**		

*Significant at the *P*<0.1 level in univariate analysis, **Significant at the *P*<0.05 level in multivariate analysis. CI – Confidence interval; OR – Odds ratio

Table 6: Comparison of performance and results of three binary logistic regression models obtained for each of the voice evaluation methods (acoustic analysis, Persian Voice Handicap Index questionnaire, and perceptual evaluation based on grade, rough, breathy, asthenia, and straining scale)

Binary logistic regression models	Percentage accuracy	Sensitivity	Specificity	AUC	95% CI	
					Lower bound	Upper bound
Acoustic analysis	84.3	87.2	82.1	0.927	0.866	0.988
VHI questionnaire	72.4	83.3	75.1	0.763	0.648	0.878
GRBAS	77.1	81.1	72.7	0.797	0.685	0.909

VHI – Voice Handicap Index; GRBAS – Grade, rough, breathy, asthenia, and straining; AUC – Area under curve; CI – Confidence interval

Dosimetric predictors for laryngeal edema after radiotherapy showed that at mean doses higher than 43.5–44 Gy, edema of Grade II or higher occurs.[29]

Based on DVH data, 39 (55.71%) patients had a mean laryngeal dose of higher than 44 Gy. In these patients, the values of the perturbation parameters increased which was an indication of edema in the vocal cords.

Six months after treatment by reducing the side effects of treatment on the larynx, the values of acoustic parameters were reduced but do not return to baseline level. HNR values increased at the end of treatment.

In general, there are vocal problems that none of the instrumental and visual methods can recognize and only the patient can understand intrinsically which needs to be noted.

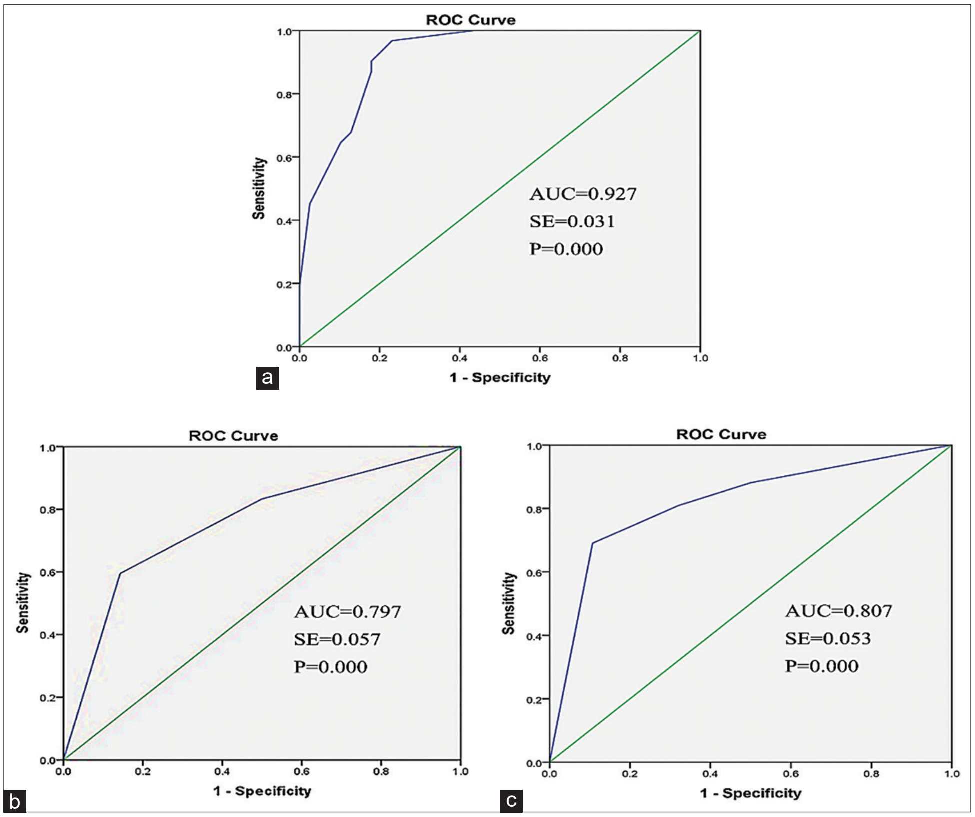

Figure 2: Receiver operating characteristics diagrams to compare the performance of each binary logistic regression models in correctly diagnosing damaged patients: (a) Based on acoustic analysis; (b) Based on Persian Voice Handicap Index questionnaire; (c) Based on GRBAS (G: Grade, R: Rough, B: Breathy, A: Asthenia, and S: Straining) scale

The Persian VHI questionnaire is a valuable tool for evaluating these problems and the patient's quality of life (QOL).[15,30,31]

An increase in VHI questionnaire scores is consistent with the increase in the rate of vocal problems and reduced voice-related QOL.[7] In the final evaluation, 42 (60%) of patients believed that their voice was different than before and complained of voice problems such as breathiness and hoarseness. In the present study, most of the patients had tumors above of hyoid bone (oropharyngeal, base of tongue, tonsil, and nasopharyngeal). RT affects the speech of patients with tumors above the hyoid bone more than voice.[8]

The patient's speech was examined by counting the numbers from 1 to 10, and reading the standard text of the "Pedarbozorg". The results of the latest evaluation by two experienced speech therapists based on the GRBAS scale showed that 37 (53%) of patients had speech problems. The results obtained from the subjective evaluation revealed that the majority of patients with higher VHI scores also had a larger G value in perceptual evaluation. These results were in agreement with the results of previous studies.[12,30]

One of the problems of patients following the RT is the complications caused by treatment and the consequent decrease in QOL. Hence, anticipating the incidence of damage for each patient will be valuable. A predictive model based on LR for radiation pneumonitis in patients receiving modern chemo-RT for the treatment of locally advanced nonsmall-cell lung carcinoma (NSCLC) was developed by Palma. They concluded that the type of chemotherapy regimen, dosimetric parameters, and patient age were the important factors in the incidence of NSCLC.[32] Langendijk *et al*. found that swallowing dysfunction can reduce the patient's QOL even more than xerostomia. Therefore, they tried to develop a model that can be easily used in clinical applications and predict dysphagia in patients under RT. Multivariate analyses of LR showed that T classification (T1–T4), neck irradiating (ipsilateral or both), weight loss, primary tumor site, and treatment modality such as conventional, accelerated, and concomitant chemotherapy were the important factors.[33]

In this study, for three models, multivariate analysis according to the Enter method of BLR showed that mean doses of larynx and chemotherapy were the most influential variables and had higher OR. In the first model, based on acoustic analysis, in addition to the mean dose of larynx and chemotherapy, V50 Gy had a significant level ($P < 0.05$, OR = 14.292). According to quantitative analyses of normal tissue effects in the clinic criteria, a dose of 50 Gy at 27% or larger volume of the larynx causes damage.[34]

In the third model, based on GRBAS, the gender factor had a significant level ($P < 0.05$, OR = 5.656). Investigators indicated that gender cannot be an important factor in the occurrence of damage.[23] The unequal number of male and female patients, heterogeneity and diversity in types of HNCs, and evaluation based on individual judgment may be the reasons for the difference between these results with other studies.

The results of Table 6 and the ROC diagrams in Figure 2 show that the model obtained based on acoustic analysis has the highest sensitivity, accuracy, and specificity, and the models based on subjective evaluations have provided almost identical results. Wide-field radiation in the 3D-CRT increased the OARs dose as well as larynx. The use of Intensity modulation RT and TomoTherapy techniques can reduce the dose of OARs and side effects of treatment and maintain the patient's QOL at an acceptable level. Accordingly, these results suggest the use of modern RT methods, increased sample size and long-term follow-up can lead to better outcomes.

Conclusions

Chemo-RT in patients with nonlaryngeal tumor HNCs can damage the larynx, thus causing vocal problems. Acoustic analysis, perceptual evaluation, and patient self-assessment are the best assessment methods due to their cheapness, noninvasiveness, high repeatability, and quantitative and qualitative evaluation of voice. Based on BLR analysis, the factors such as chemotherapy, mean dose of larynx, V50 Gy, and gender had the greatest effect on laryngeal damage and the regression model based on acoustic analysis had the best performance in classifying patients in affected and normal groups.

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Conflicts of interest

There are no conflicts of interest.

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