Original Article

Radiation-Induced Complication after Radiotherapy in Patients with Head-and-Neck Cancers

Abstract

Background: Exposure of nontarget organs such as the thyroid gland (as a normal and high radiosensitive tissue) to radiation during radiotherapy for patients with head-and-neck cancers remains unavoidable. Hypothyroidism is the most common radiation side effect on the thyroid gland. In this study, we used the parameters of thyroid gland (triiodothyronine [T3], thyroxine [T4], and thyroid-stimulating hormone [TSH]) measurements before and after radiotherapy for patients with head-and-neck cancers. **Materials and Methods:** In the first step, descriptive statistics for predictors and response variables were performed. In the next step of data analysis, a multivariate linear mixed-effects model was fitted simultaneously for three response variables in order to study the trend of thyroid gland parameters. **Results:** The results indicated that there was a significant decreasing trend in TSH from 1.74 at baseline to 0.65 at the end of the study, and there was a significant increasing trend in T4 from 8.63 at baseline to 9.38 at the end of the study. **Conclusions:** There were significant changes in thyroid gland parameters after radiotherapy treatment for patients with head-and-neck cancers. Thus, preventative strategies are needed to reduce this complication. The patients with head-and-neck cancers who received radiotherapy treatment should be evaluated regularly and repeatedly during the radiotherapy treatment period.

Keywords: *Complication, head-and-neck cancers, longitudinal data, multivariate mixed-effects model, trend*

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Introduction

Head-and-neck cancers are among the most common cancers in the world.[1] Cancers, which are known collectively as head-and-neck cancers, are usually a group of cancers that start in the mouth, nose, throat, larynx, sinuses, or salivary glands. Head-and-neck cancers include approximately 2%–5% of neoplasms.[2] These types of cancers are more prevalent in men.[1,2] Most of diagnosed patients were over 40 years old.[2] Alcohol and tobacco use are the two most important causes of these cancers. At least, 75%–80% of head-and-neck cancer incidence are due to these two risk factors. In case of using both tobacco and alcohol together, the risk of these cancers' development is far greater than its single use.[1,2]

During the past 20 years, it has been evident that a subset of head-and-neck squamous cell carcinoma can be the result of human papillomavirus (HPV) in addition to genital and anal cancers. The HPV, while an infection forms, can cause different types of head-and-neck cancers; tonsil and tongue base are the most affected regions.[3-6]

Radiotherapy, surgery, and chemotherapy are the three main types of treatment to control and manage head-and-neck cancers.[7] Choosing the best and proper treatment method depends on several factors, such as "type and stage of head-and-neck cancers, possible side effects, and patient's preferences and overall health." Radiotherapy is a single-modality treatment in early and low-staging head-and-neck cancers.[8] The main goal of radiotherapy is to maximize damage to all cancer cells and to minimize damage to healthy tissues around the tumor. To achieve this goal, the treatment planning must be performed based on the highest tumor control probability and the least normal tissue complication probability.[9]

Unfortunately, nontarget organs such as the thyroid gland (as a normal and high radiosensitive tissue) exposure to radiation

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during radiation therapy for patients with head-and-neck cancers remains unavoidable.[10] In the literature, hypothyroidism, hyperthyroidism, benign adenoma, Graves' disease, and even thyroid cancer have been reported as late effect complications due to radiotherapy. Hypothyroidism is the most common side effect of radiation on the thyroid gland. Hypothyroidism has a wide range of incidence varies from 3% to 92%, but its incidence is more probable in the range of 15%–48% after using treatment for these types of cancers.[11]

In order to investigate thyroid toxicity in head-and-neck cancers, it is necessary to measure parameters of the thyroid gland such as thyroid-stimulating hormone (TSH), T3 (triiodothyronine), T4 (thyroxine), free triiodothyronine (FT3), and free thyroxine (FT4) before and after radiotherapy. To assess the trend of change, these parameters should be repeatedly measured in different time points (longitudinally).

Our literature review revealed several published articles about late effect complications on the thyroid gland, especially hypothyroidism as a common radiation side effect during the period of head-and-neck areas radiotherapy. For this purpose, all articles used univariate statistical models; the researchers of the present study did not find any published manuscript on assessing the trend using multivariate statistical models. Therefore, this study was performed to assess the trend of all parameters of the thyroid gland and its related factors simultaneously. To do this end, we utilized multivariate longitudinal methods.

Accordingly, appropriate statistical models should be utilized to analyze these kinds of data sets. In this context, Multivariate linear mixed effects models (MLMMs) are among the most common approaches used. This model (MLMM) has flexibility in accounting different levels of within-subject variability and considering multiple response variables.[12]

Materials and Methods

In this study, the thyroid gland parameters were regarded as the response variables under study. The study included prospective analysis of fifty patients with consecutive head-and-neck cancers to investigate their thyroid toxicity during and 1 year after their treatment at a radiation therapy department in a hospital in Tehran (the capital city of The Islamic Republic of Iran). The serum samples, the echo level, and the color Doppler parameters of the thyroid gland were also measured before and at regular time intervals during and after the radiotherapy (eight times).[9] Furthermore, at the beginning of the study, other information of patients such as age and sex were also collected.

The main objective of this study was to assess the complication of the thyroid gland during and after radiotherapy for 1 year of the study.

Statistical analysis

The Linear mixed effects models (LMMs) are extensions of simple linear models that contain both random and fixed effects. A fixed effect is a parameter that does not vary. Fixed effects are population characteristics that are assumed to be shared by all individuals. Random effects are subject-specific effects that are unique to a particular individual. Inclusion of these two distinct parts in the model allows the data analysts to consider both between-subject and within-subject sources of variation in the longitudinal responses. The linear mixed models (LMMs) are useful methods for analyzing nonindependent, longitudinal, or correlated data.[13]

Suppose Y_{ij} is the response for the i^{th} sampling unit in j^{th} occasion, β is a $(P \times 1)$ vector of fixed effects, b_i is a $(q \times 1)$ vector of random effects, X_i is a $(n_i \times p)$ matrix of covariates, Z_i is a $(n_i \times q)$ matrix of covariates, with $q \leq p$ (the columns of Z_i are subsets of the columns of X_i), and e_i is $(n_i \times 1)$ vector of error term,[13] the general form of LMMs can be written as follows:

$$Y_i = X_i\beta + Z_i b_i + e_i \quad (1)$$

The random effects, b_i, are assumed to have multivariate normal distribution with mean zero and covariance matrix G ($b_i \sim MVN\,[0, G]$). The error term, e_i, is assumed to have normal distribution with mean zero and variance R_i ($e_i \sim N\,[0, R_i]$).[13]

Amrik *et al*. extended the linear mixed-effects models (equation 1) of a single response variable to the case of multiple response variables.[12] In this case, a matrix of response variables is used instead of a vector of response variable for every patient.

y_{ijk}: i^{th} subject ($i = 1,\ldots, N$), j^{th} outcome ($j = 1,\ldots, r$), k^{th} occasion ($k = 1,\ldots, s_i$)

$$Y_i = \begin{pmatrix} y_{i11} y_{i21} \cdots & \ldots \cdots & y_{ir1} \\ y_{i12} y_{i22} \cdots & \ldots \cdots & y_{ir2} \\ y_{i1si} y_{i2si} \cdots & \ldots \cdots & y_{irsi} \end{pmatrix}$$

The trends with different starting points were measured before the start of radiotherapy; these trends were seen separately for each response variable in the trajectory plot of these patients. Furthermore, in order to determine the effect of head-and-neck areas' radiotherapy on the thyroid gland, the fitted multivariate linear mixed-effects models (MLMMs) with intercept random effect were as follows:

$$Y_{ij} = \beta_0 + \beta_1 \times Sex_{ij} + \beta_2 \times Age_{ij} + \beta_3 \times Time_{ijk} + b_{0i} + e_{ij} \quad (2)$$

y_{ijk}: i^{th} subject ($i = 1,\ldots, 50$), j^{th} outcome (j = 1:T3, 2:T4, 3:TSH), k^{th} occasion ($k = 1,\ldots, 8$)

In this model,[2] every patient has an underlying level of response overtime period ($\beta_0 + b_{0i}$). Here, we allow the intercept to vary randomly from one patient to another.

The statistical analyses were performed using the R software, Version 3.3.2, R development core team, University of Auckland, New Zealand.

Results

In this study, we assessed fifty patients with head-and-neck cancers, who received radiotherapy as the main or complementary medication. All fifty patients had a complete follow-up (before and during radiation therapy) for 1 year. The parameters of the thyroid gland for patients with head-and-neck cancers under radiotherapy treatment were measured. The baseline thyroid gland's parameters were evaluated; these measurements were obtained for each patient at the end of the 1st, 5th, 10th, 15th, 20th, 25th, and 30th radiotherapy treatment sessions.

The mean and standard deviation of these patients' ages was 55.62 ± 12.46, ranging from 28 to 86 years old. Among them, 18 (36%) patients were female and 32 (64%) patients were male. The dose per fraction was 1.8–2 Gy. For 41 (82%) patients, the dose per fraction was 2 Gy and for others was 1.8 Gy. The mean and standard deviation of mean dose to thyroid of these patients was 4232 ± 1290, ranging from 1300 to 6500 cGy.

The trends of the response variables' mean and standard deviation of the patients under study are shown in Table 1. According to the information of Table 1, there was a significant decreasing trend in TSH from 1.74 at baseline to 0.65 at the end of the study. There was a significant increasing trend in T4 from 8.63 at baseline to 9.38 at the end of the study. Furthermore, Figure 1 shows the obtained results.

In the next step of data analysis, we fitted the described multivariate mixed-effects model to the data. To assess the trend of changes in thyroid gland parameters, a multivariate mixed-effects model with random intercept was fitted simultaneously for T3, T4, and TSH adjusting for sex and age.

Furthermore, assessing the trend of changes in the thyroid gland for each response variable revealed that T4 had the highest and TSH had the lowest intercepts at the start point of the study. The significant variance of random term showed a remarkable heterogeneity in parameters of the thyroid gland among these patients with head-and-neck cancers at the baseline. Table 2 shows the obtained results.

The negative sign of session estimate indicated a reduction in the amount of TSH over the time of the study. The positive sign for the session estimate indicated an increase in the amount of T4 over the time of the study.

Discussion

In this study, we aimed to determine the trend of thyroid gland parameters (T3, T4, and TSH) during head-and-neck

Table 1: Mean±standard deviation of parameters of the thyroid gland of patients under study

Test	Baseline	5th session	10th session	15th session	20th session	25th session	30th session	*P**
T3	1.23±0.29	1.24±0.21	1.23±0.24	1.20±0.22	1.18±0.24	1.21±0.22	1.25±0.25	0.67
T4	8.63±1.68	9.15±2.11	9.07±2	9.15±2.18	9.30±2.27	9.38±2.28	9.38±2.19	0.001
TSH	1.74±1.2	1.36±1.1	1.03±1.14	0.85±0.81	0.78±0.91	0.72±0.95	0.65±1	<0.001

*From the repeated measures analysis. TSH: Thyroid-stimulating hormone

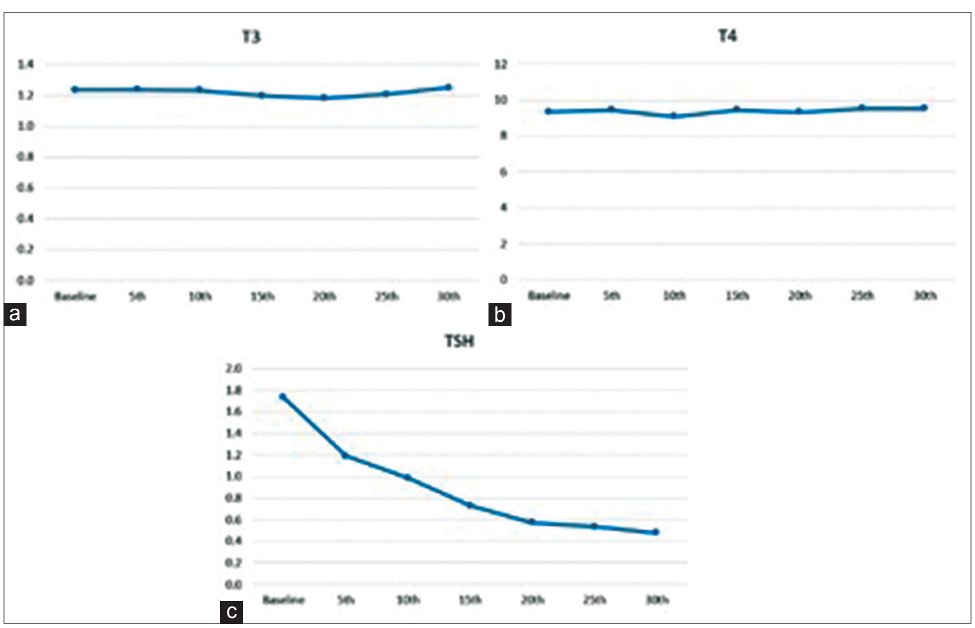

Figure 1: The trend of the response variables' mean during study time for triiodothyronine (a), thyroxine (b), and thyroid-stimulating hormone (c)

Table 2: Estimated from the multivariate mixed-effects model

Dependent variable	Independent variable	Estimate	SE	*P*
T3	Intercept	1.421	0.469	0.002
	Sex*	0.052	0.208	0.804
	Age	−0.004	0.008	0.615
	Session	−0.005	0.007	0.939
T4	Intercept	9.869	0.469	<0.000
	Sex*	−0.306	0.208	0.141
	Age	−0.015	0.008	0.061
	Session	0.021	0.007	0.002
TSH	Intercept	0.777	0.469	0.098
	Sex*	0.157	0.208	0.449
	Age	0.012	0.008	0.141
	Session	−0.034	0.007	<0.000

*Sex: Female (0): Reference category and Male (1). SE: standard error, T3: triiodothyronine, T4: thyroxine, TSH: thyroid-stimulating. hormone

radiation therapy. Assessing the trend of response variables' mean using univariate analysis showed a decreasing trend for TSH level and increasing trends for T3 and T4 levels with significant slope for T4 and TSH and nonsignificant slope for T3. The multivariate mixed-effects model was also fitted to the response variables simultaneously which resulted in similar findings. The negative sign for the session estimate indicated a reduction in the amount of TSH level, and the positive sign for the session estimate indicated an increment in the amount of T4 level after radiotherapy treatment. Our results demonstrated that the thyroid gland parameters had been changed during the radiotherapy session.

Reviewing the previously published articles in this field showed that almost all research studies used simple statistical methods, such as the logistic regression model, the correlation test, and the Fisher's exact test to investigate side effects of radiotherapy in patients with head-and-neck cancer. For instance, Cheraghi *et al*. investigated sensorineural hearing loss (SNHL) in patients diagnosed with head-and-neck cancers who received radiation therapy using the paired sample *t*-test. They followed up 29 patients for 6 months and confirmed that hearing loss was a related side effect of radiation therapy. Furthermore, this study demonstrated that patients who had received radiotherapy and chemotherapy concurrently experienced greater SNHL compared to those received radiotherapy alone.[14] Chaibakhsh *et al*. showed a direct relationship between received dose by the ears and severity of hearing loss in these patients. In their study, 66 patients with head-and-neck cancers treated by radiotherapy were investigated for 1 year.[15] In another study, Rabiei *et al*. assessed the complications of postradiation on 45 patients with head-and-neck cancers in a follow-up study. They reported that the subjective complains were increased 1 month after radiotherapy and then reduced to initial status 3 months after radiotherapy. Xerostomia, dysphagia, trismus, and dysgeusia were significantly greater 1 month after posttreatment comparing to 3 months after radiotherapy. They reported that pain in ear and jaw had a significant correlation with radiation dosage in their research.[16]

Many studies reported thyroid disorders such as hypothyroidism, hyperthyroidism, Hashimoto thyroiditis, Graves' disease, benign adenoma, and thyroid cancers as more prevalent different radiation-induced late effects.[11,17,18] Among them, hypothyroidism is one of the most frequent thyroid late effects in head-and-neck cancer patients treated with radiotherapy.[11,17] Grande applied multiple logistic regression to evaluate the risk factors related to hypothyroidism after radiotherapy for head-and-neck cancers. He used factors such as radiation dose to the thyroid region, combination of cervical surgery, shielding of midline, and interval radiation study as independent variables in multiple logistic regression. In this study, the estimated radiation received dose by the thyroid region showed a significant effect on the incidence of hypothyroidism.[19] Bakhshandeh *et al*. studied some thyroid disorders during head-and-neck radiotherapy using repeated measures analysis and bivariate correlation tests. They concluded that there were significant changes in TSH, T4, and FT4 levels, but no significant changes in T3 and FT3 levels after radiotherapy course. The results of this study showed decreasing trend for TSH and increasing trend for T4 and FT4.[10] Ghapanchi *et al*. used the t and Chi-square tests to evaluate thyroid disorders during head-and-neck radiotherapy. They concluded that providing management plans before and after treatment seems necessary due to radiotherapy high complications.[2] Feen Rønjom conducted another study in head-and-neck patients in order to determine some important side effects of radiotherapy. The first study was a retrospective cohort study, second and third studies were validation. They used the logistic and multivariate mixture models to analyze data. The results showed that hypothyroidism was a frequent late effect after definitive radiotherapy.[20] Alterio *et al*. performed a retrospective data evaluation of 73 patients treated for head-and-neck cancers; they reported hypothyroidism as the most prevalent thyroid side effects in patients treated with radiotherapy using the Fisher's exact test.[17] Regarding the above-mentioned studies, hypothyroidism could be thought as the most common side effects of the radiation therapy in head-and-neck cancer patients.

Multivariate analysis is a set of statistical methods used to analyze data sets with more than one response variable, especially in correlated response data. Multivariate linear mixed-effects models are flexible statistical tools which allow us to include additional regression coefficients for considering the heterogeneity between patients under study. It means that some subsets of the regression coefficients vary randomly from one individual to another.

The advantage of the present research was utilizing more complex statistical modeling approach to analyze data. This model helped us to capture the relationship between radiotherapy and thyroid gland parameters more efficiently. Small sample size may be considered as the most important limitation of our study.

Conclusions

In general, our findings indicated that the thyroid gland parameters were affected by the radiotherapy during head-and-neck cancer treatment. Thus, these patients need regular thyroid gland factor evaluations by the endocrinologist. In addition, increasing the number of radiotherapy sessions leads to more significant changes in thyroid gland parameters. Thus other studies with adequate sample size should be conducted to identify other potential side effects of radiotherapy (such as benign adenoma, and thyroid cancer) in order to promote the level of care in patients with head-and-neck cancers.

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Conflicts of interest

There are no conflicts of interest.

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