Original Article

Thyroid Dose and Hypothyroidism as a Result of Radiation Therapy for Head and Neck Malignancies and Brain Tumors in Iran

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Head and Neck Tumors.

Abstract

Purpose: Radiation Therapy has a fundamental role in the treatment of cancer. Achieving Tumor Control Probability (TCP), while avoiding normal tissue complication is the goal of this treatment modality. The sensitivity of the thyroid gland to radiation increases the risk of developing secondary thyroid cancer and hypothyroidism.

Materials and Methods: The average dose to the thyroid from head and neck irradiation was measured using in vivo dosimetry (Thermolumincsence Dosimetry). The Radiotherapy technique was given using 6 MV x-rays from an Elekta compact linear accelerator and conformal technique delivered 1.8 to 2.0 Gy over 5 sequential days per week.

Results: The average absorbed dose to the thyroid from head and neck radiotherapy was 4.4% of the prescription dose and from whole brain radiotherapy was 0.7% of the prescription dose. Thyroid Stimulating Hormone (TSH) levels were determined in 30 patients before and after completion of radiation therapy. The average concentration of TSH increased from 0.88 +/- 0.55 (pre-radiotherapy) to 1.7 +/- 0.66 (post-radiotherapy), ($p < 0.05$).

Conclusion: Thyroid absorbed dose was less than the threshold dose for patients who received radiotherapy to the head and neck based on thyroid function tests.

1. Introduction

The aim of this study is to determine the absorbed dose to thyroid gland when radiotherapy is applied to head and neck tumors based on in vivo measurement by luminescent dosimetry. Head and Neck (HN) cancers are the fifth most common cancers in the world [1]. The treatment of head and neck cancers utilizes surgery, Radiotherapy (RT), chemotherapy, or a combination of these. Inspite of the efficacy of radiotherapy, patients may suffer from both acute and late side effects that may affect the quality of life. The thyroid gland receives scattered radiation from within the patient body as well as machine leakage radiation during irradiation [2]. As a result, the most common late effect on the thyroid gland is hypothyroidism [3]. Hypothyroidism can be diagnosed by laboratory tests [4]. After RT of HN tumors, nearly 10 – 50% of patients develop hypothyroidism [5]. Emami *et al.* determined that the thyroid gland tolerance,TD5/5 (tolerance dose represents the radiation dose that would result in 5% risk of severe complications within 5 years after irradiation) as 45Gy [6]. Hypothyroidism is classified as clinical or subclinical. Clinical hypothyroidism is associated with an increase of Thyroid Stimulating Hormone (TSH) and with clinical symptoms, such as weight gain, cold intolerance, fatigue and others.

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Subclinical Hypothyroidism (SCH), also called mild thyroid malfunction, is diagnosed when thyroid hormone levels are within normal reference laboratory range but TSH levels are moderately elevated [7]. The mechanisms of radiation induced hypothyroidism are considered to be due to damaged thyroid blood vessels and changes in follicular cell function [8]. Several studies have estimated absorbed dose to the thyroid and correlated with the incidence of hypothyroidism, but there is still insufficient data for determining the tolerated dose of organ at risk. The objective of this research is to determine the average of absorbed dose of thyroid and hypothyroidism, as a result of radiation therapy for head and neck and brain malignancies using TL dosimetry in Ramezanzadeh radiotherapy center of Yazd.

2. Materials and Methods

This study included 50 patients; 30 head and neck patients and 20 brain patients. The head and neck tumors involved the oropharynx, hypopharynx, larynx and nasopharynx. All were treated between April and November 2016 at the Ramezanzadeh radiotherapy center of Yazd. All of the participants were between 42 and 75 years old with the mean age of 58. The patients had no previous history of thyroid disorder. 40% of the patients received concomitant chemotherapy. All patients were treated using megavoltage photons. The RT was given using 6 MV x-rays from an Elekta compact linear accelerator (made in China under license in the UK) and conformal technique delivered 1.8 to 2.0 Gy over 5 sequential days per week. The accelerator was Electa with model of compact, made in China under license in the UK. In Figure 1, patient position and the linear accelerator are shown. Head and neck radiotherapy used lateral opposed portals to the upper neck and a separate anterior portal to the lower neck. After 40 to 45 Gy, the fields are modified to protect the spinal cord. The boost field was given after the implementation of 45 Gy. The total prescribed dose for the head and neck treatment was 44-60 Gy. The whole brain irradiation was delivered with opposed lateral fields and the prescribed dose was 30 Gy in 10 fractions. CT based virtual simulation was performed for all patients and a custom mask used for immobilization (during imaging and treatment).

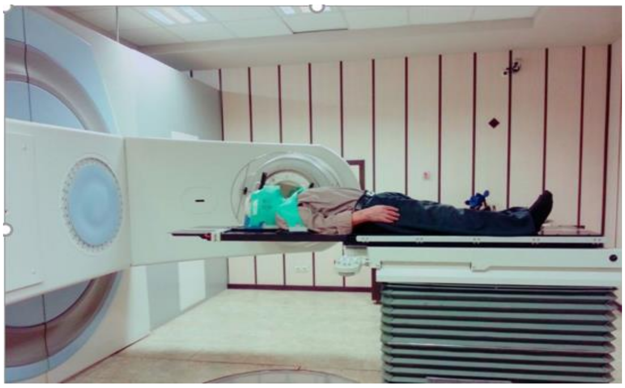

Figure 1. Patient position in the compact linear accelerator

2.1.Thermoluminescent Dosimetry (TLD)

In vivo dose measurements were obtained for three fractions during the course of external beam radiotherapy. The average of these doses was expressed as the measured dose per fraction. In Figure 2. TL chip locations are displayed. The TL chips were placed on the skin surface and 1cm thick bolus material applied to determine the maximum dose. Unlike most studies that report measured dose to the thyroid from all fields, in our study, we evaluated scatter dose to the thyroid from each field separately. Thyroid was not in lateral field, but in anterior beam thyroid was in the field. Key factors in TL dosimetry are high sensitivity and effective atomic number close to that of tissue. The TLD results were obtained using 4.5 mm diameter x 0.8 mm thick solid chips (GR200, LiF: Mg, Cu, P) and an automatic TL Reader model of 7103 made in Iran. The TLD readings were used to determine absorbed dose. Annealing was done at 240° C for 15 secs. In this paper, we had to use 1 centimeter bolus to determine absorbed dose of thyroid. The Time Temperature Profile (TTP) was set at an initial preheat temperature of 135˚c, with rate of 6˚c/s for 18 secs. The TLD chips that were selected for this study had demonstrated reproducibility within 2.7%. The TLD was calibrated using 6 MV X-ray based on Scdx-Wellhofer FC65-G ionization chamber. In order to determine dose values, a calibration curve was plotted in which the TLD reading in nano Coulomb (nC) is related to absorbed dose in cGy. The TLDs displayed a linear dose response (R2 = 0.998) with respect to the measured dose over a range of 2 to 24 cGy. The calibration curve is shown in Figure 3. For determination of TLD dose we used an Element Correction Coefficient (ECC). ECC is a correction factor which relates the TL efficiency of a specific dosimeter to the average TL efficiency. The absorbed dose was obtained using the following formula:

$$Absorbed\ dose = TLD\ reading\ (nC) \times ECC \times Calibration\ factor\ (cGy/nC)$$

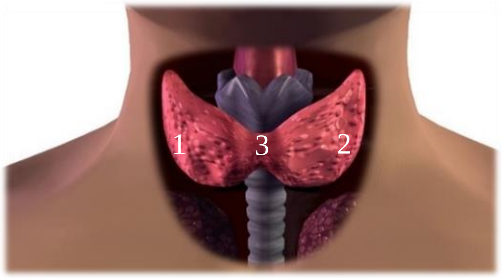

Figure 2. Position of TL chips at the left and right thyroid lobes (points 1 & 2) and along the midsagittal line (point 3)

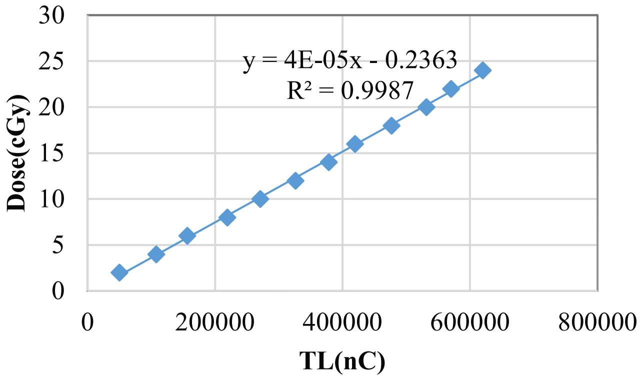

Figure 3. TLD calibration curve base on relation of dose (cGy) to TL counts (nC)

2.2.Treatment Planning System

CT virtual simulation used 5 mm slice thickness from a two slice scanner, Siemens CT made in China. The CT images were transferred to the planning system in (DICOM) format, digital imaging and communication in medicine. All patients were treated using 3D conformal radiotherapy. After contouring the thyroid glands on the CT images, the dose distribution and absorbed dose to the thyroid were analysed via Dose Volume Histograms (DVH). Data output included thyroid volume and thyroid gland dose as computed by the Prowess Treatment Planning System (Panther, version 5.2).

2.3.Thyroid Function Evaluation

The TSH test was done before the start of radiotherapy and at the end of treatment for all patients. Blood samples (3cc) were obtained with patient permission. The serum and plasma were separated by centrifugation. A variety of methods are used to assess TSH, but in this paper the estimation was done using immune radiometric assay. Hypothyroidism is defined as TSH level above 5 µUI/mL[9].

2.4.Statistical Analysis

All statistical analyses were carried out using SPSS 16.0 software. Word and Excel were used to generate graphs, tables, etc. Paired t-test was used to compare the significance between TSH before and after the radiotherapy. Significance levels were set using p-value of 5%.

3. Results

The average measured thyroid dose due to scattered radiation from opposed lateral fields was 8.75 cGy that means 4.37% of the prescribed dose per fraction. The average dose received by the thyroid in 30 patients from three fields (two lateral fields and an anterior field) was 143.8 cGy per fraction which is 71.9% of prescribed dose in three fields.

The average thyroid dose in 20 patients, who received radiotherapy for brain cancer, was 2.11 cGy per fraction or 0.7% of prescribed dose.

In Figure 4, there is a clear trend of decreasing dose with distance between the thyroid glands and the field edge.

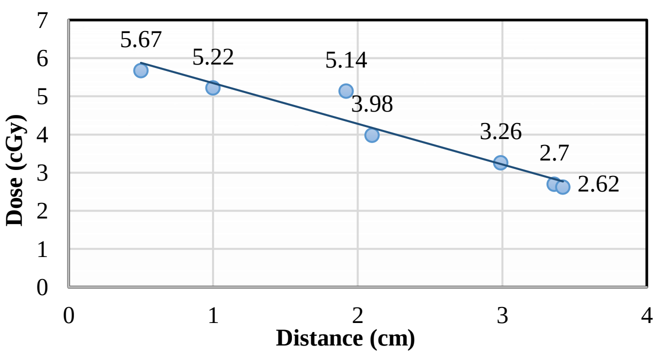

Figure 4. Relationship between absorbed dose and distance of thyroid glands from field edge

Table 1. Treatment characteristics of the 50 patients are shown in table

patient frequency with Head & neck tumors	30
patient frequency with Bain tumors	20
Male	29
Female	21
Median age	58 years
Range of age	42-75 years
Frequency of heal & neck tumors:	
Nasopharynx	3
Tongue	7
Larynx	6
Mouth	1
Sinus	2
Lip & jaw & mandible & salivary	5
Hypopharynx	1
Brain	20
Frequency of III malignancy Stage	25
Frequency of IV malignancy Stage	5
Treatment Only by radiotherapy	60%
Radiotherapy and chemotherapy	40%
Mean thyroid volume	17.76 cc
Total prescribed dose	4400 cGy
Mean thyroid dose	3164 cGy
Mean thyroid dose of scattering by TL dosimetry	8.75 cGy/fraction

The absorbed dose results as a function of the radiation field size in the Compact accelerator for the 6 patients are shown in Fig. 5. The results show that as the field size increases, the absorbed scatter dose is increased. Table 2 Shows, the effect of the radiation on TSH concentration of patient serum and thyroid function test before and after the course of RT, ($p<0.05$). Fig. 6 shows how the concentration of TSH following RT was affected.

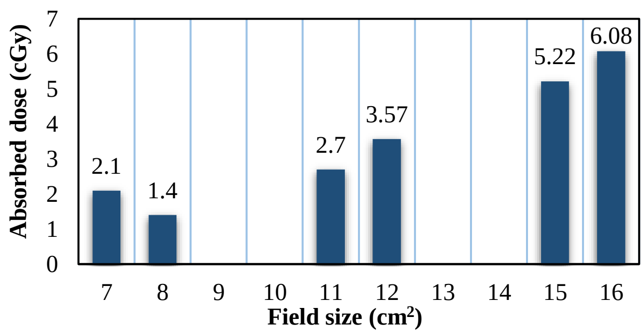

Figure 5. The effect of X-ray field size on the absorbed dose of thyroid in Compact radiotherapy machines for 6 patients

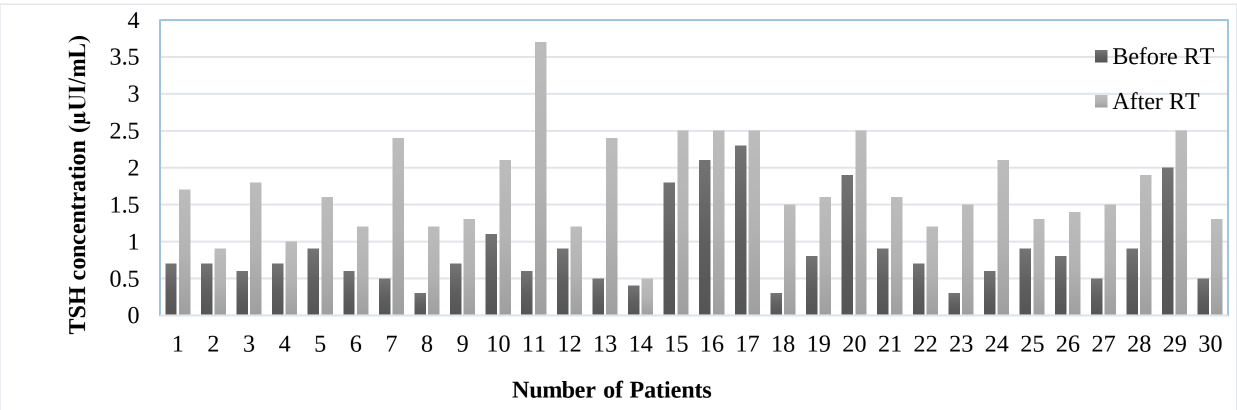

Figure 6. TSH concentration in the serum of patients before and after RT courses

Table 1. The effect of the radiation on TSH concentration of patient serum and thyroid function test before and after the course of RT

Test	Mean ±SD, before RT	Mean ±SD, after RT	P – value
TSH	0.88 ± 0.55	1.7 ± 0.66	P<0.05

4. Discussion

One of the most important treatment goals of radiotherapy is to deliver sufficient dose to the tumor and minimize dose to healthy tissue. Radiotherapy may cause various thyroid disorders and jeopardize the patient's quality of life. Thyroid is one of the radiosensitive organs in the body. These disorders include primary and central hypothyroidism, thyroiditis, Graves' disease, benign adenoma, nodular goiter or carcinoma [9]. The aim of this research was to determine the average of absorbed dose of thyroid and hypothyroidism, as a result of radiation therapy for head and neck and brain malignancies. Many studies rely on phantoms to estimate absorbed dose to the thyroid from scattered X-rays [10]. The present discussion focuses on in vivo dosimetry in conformal radiotherapy technique. We should note that more advanced techniques such as IMRT and VMAT are popular in the head and neck radiotherapy and they can spare thyroid, but we have not yet implemented these techniques in our center. Magdalena p. studied doses in organs at risk during head and neck radiotherapy using IMRT and 3D-CRT, the results of this study demonstrate that organs located outside of the IMRT beam were thought to be well-spared [11]. The dose is from leakage radiation and scatter radiation from the accelerator and from within the patient. TLD measurements on patients were carried out to calculate the average of absorbed dose of thyroid. We have determined the average dose received by the thyroid glands from two opposed lateral fields to be 0.087 Gy in head and neck treatment with 2Gy per daily fraction or 4.37 % of the prescribed dose. The 3D-CRT patients received conformal radiation therapy for 44 Gy in 22 fractions. Studies by Attia Gul have shown dose received by thyroid in radiation neck fields (two lateral fields and an anterior field) was 55 to 100% of prescribed dose. Average dose of thyroid was 44.38 Gy in total therapy sessions [12]. In another research it has been shown that direct irradiation of thyroid with total doses of 26 to 30 Gy can lead to functional abnormalities [13]. Ahmad M. found that mean thyroid dose ≥ 34 Gy had a significant impact on the development of HT [14]. In our review, thyroid dose was 32 Gy. The difference in the amount of dose is because of several reasons such as type of device, type of equipment, techniques and shielding. In 1991, Emami *et al.* calculated tolerance dose of critical organs. The value of TD5/5 for thyroid is 45 Gy [6]. TD5/5 is the dose that causes 5% probability of a complication in the 5 years following treatment. Based on the threshold dose that has been noted to cause hypothyroidism, thyroid dose of 32 Gy in Ramezanzadeh radiotherapy center seems desirable although the doses of 10 cGy caused an increased risk of thyroid cancer [15]. In this study, doses from cranial radiation scattered to the thyroid by lateral fields were also determined. With Dosimetry on 20 patients with brain cancers with prescription dose of 30 Gy in 10 sessions, the average thyroid dose was 2.1 cGy/fr (0.7% of prescription dose. Attia Gul investigated thyroid dose of cranial irradiation that was 0.52 Gray (1-3% prescribed dose) [12]. Kalliopi M. reported thyroid dose received by the brain scattered 0.42% [16]. A number of studies have measured scattered dose to the thyroid at different distances from the lower lateral fields that correspond with the results of this study. In present study with distance from the edge of the lateral field, thyroid dose was reduced. Stevens studies showed that thyroid dose was decreased with increasing of distance from the lower edge of the field [2]. In Figure 5 it has been shown that thyroid absorbed doses increasing with field size. The results of hormone tests are shown in Table 2. The results of this study clearly demonstrate rising TSH following radiation to the thyroid. The average concentration of TSH before radiotherapy was 0.88±0.55 and after completion of treatment was 1.7±0.66. The P - value Statistical test using paired t - test was <0.05. Thus, the change in thyroid hormone before and after radiation therapies was significant. In a study by Akim M., doses up to 26 Gy were in 44% of patients. In this study, the dose of thyroid in supraclavicular fields in the treatment of breast was evaluated. The average dose received by the thyroid in this study was 22.5 Gy [13]. Another study was conducted by Miyawaki D. in patients with head and neck cancers to check hypothyroidism. Analyzed data from 80 patients with oropharynx and hypopharynx cancers concluded that radiation therapy leads to hypothyroidism in 51.8% of patients. Mean follow-up duration was 49 months. They reported that the average time to create hypothyroidism was 2-55 months after radiotherapy [17]. In a study by Garcia Serra *et al.* it has been recommended that the level of TSH shall be assessed every 6 months during the first year of treatment and then be done annually [18]. Bruning *et al.* showed that primary hypothyroidism can occur after irradiation of supraclavicular field in patients with breast cancer [19]. The report made by Williams E.D. *et al.* indicated that high levels of TSH in serum would increase the risk of thyroid cancer [20].Thus the various reports recommended continuous monitoring of serum TSH after radiotherapy. The lack of data about the follow-up patients regarding the thyroid functions was the main limitation of our study. However, our aim was to assess the thyroid doses during 3D-CRT planning using TL dosimetry in which all head and neck patients received irradiation.

5. Conclusion

We have demonstrated at the radiotherapy center of Yazd that the thyroid can receive up to 4% of the prescribed dose from head and neck irradiation and 0.7% of the prescribed dose from cranial radiotherapy. Due to the sensitivity of the thyroid, this study suggests that thyroid should be shielded or excluded from the field as much as possible and all patients undergoing radiotherapy of head and neck should have thyroid function monitored. This study demonstrates that TSH concentration increases after RT. We recommend that thyroid function and symptoms of hypothyroidism should be evaluated after RT until it disturbs the patient's daily life in Shahid Ramezanzadeh Radiotherapy Center of Yazd. Further studies should be done in order to demonstrate the correlation between thyroid functions and dose of radiation in patients with head and neck cancer.

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