Original Article

DOI: 10.7860/JCDR/2025/74393.21162

Biochemistry Section

Thyroid Hormone Levels in Patients with Head and Neck Cancer Undergoing Radiochemotherapy: A Retrospective Study

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ABSTRACT

Introduction: Head and Neck Cancers (HNCs) are a common type of cancer, affecting approximately 6% of the global cancer burden. The treatment of HNC often involves Radiochemotherapy (RCT), which can have adverse effects on the thyroid gland. The present study investigates how RCT impacts thyroid function in patients with HNC.

Aim: To determine the effect of RCT on Thyroid Stimulating Hormone, (TSH) triiodothyronine and thyroxine.

Materials and Methods: This was a retrospective study conducted in Department of Biochemistry at Medical College and SSG hospital, Baroda, Gujarat, India. Data of patients were collected from radiology department from period of January 2016 to April 2017. Patients who were initially euthyroid were included in present study (N=59). Thyroid levels were tested by immunoassay. Mean and standard deviation were calculated and statistical analysis was done using the Analysis of Variance (ANOVA) test.

Results: The mean±Standard Deviation (SD) of various thyroid function levels before and after 1, 3, and 6 months of RCT were; serum T3=1.2±0.4, 1.6±0.5, 1.3±0.6 and 0.7±0.4 ng/mL, respectively, serum T4=9±2, 11±3, 8±2 and 5±1 µg/dL respectively and serum TSH=2.4±1.5, 1.9±1.5, 4.4±1.1 and 6.9±1.7 mIU/mL respectively. Serum T3 and serum T4 increased significantly after one month (p=0.008 and 0.004) and decreased significantly after six months of treatment (p=0.0001) whereas, serum TSH increased significantly after three months (p=0.015) of treatment.

Conclusion: It was concluded that treatment of HNC with RCT may affect thyroid functions. There is a tendency to develop hyperthyroidism initially after one month of RCT, but later on, Hypothyroidism (HT) develops. So, it is advisable to test the thyroid profile on regular follow-up to enable early diagnosis and treatment of any thyroid malfunction that can develop after RCT.

Keywords: Hypothyroidism, Triiodothyronine, Thyroid dysfunction, Thyroid stimulating hormone, Thyroxine

INTRODUCTION

The thyroid gland, which is situated in the anterior neck, and directly in front of the trachea, is the biggest endocrine gland in the human body. Its primary job is to secrete triiodothyronine (T3) and thyroxine (T4), two thyroid hormones that are essential for healthy growth and development. These thyroid hormones are responsible for regulating the metabolism of various tissues, ensuring that they function optimally. TSH, which is generated and released by the anterior pituitary gland in response to signals from the hypothalamus, is the main regulator of thyroid hormone output. The thyroid gland is stimulated by TSH and releases T3 and T4 in the proper amounts to maintain general physiological balance [1,2].

Otolaryngological, oral, and maxillofacial cancers, as well as neck cancers, comprise HNC, which make up around 6th most common of all malignant cancers globally [3]. The oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, soft-tissue, neural structures, and glands like the salivary, thyroid, and parathyroid glands are just a few of the places in the head and neck region where these malignancies can develop [4,5]. A significant challenge in the management of HNC is that the majority of these tumors have already spread locally and regionally by the time they are diagnosed.

The treatment of HNC typically involves a combination of different modalities, including; surgery, Radiation Therapy (RT), Chemotherapy (CT), and a combination of both known as Radiochemotherapy (RCT) [6]. RT can cause progressive condition known as "Radiation Fibrosis Syndrome" (RTFS) can be brought on by damage to blood vessels that supply muscles, neurons, and bones. This can lead to a number of issues [7]. The RT for HNC might have two different kinds of adverse effects: early side-effects and late side-effects. Late side-effects include lymphedema; HT, hyperparathyroidism; lightheadedness, dizziness, and headaches; secondary cancer; and damage to the eye, ear, nervous system, and neck structures. Osteoradionecrosis, pharyngoesophageal stenosis, dental caries, oral cavity necrosis, fibrosis, radiation recall myositis, impaired wound healing, skin changes and skin cancer [8,9].

The major form of treatment for HNC is RCT, the most prevalent kind of radiation-induced thyroid dysfunction is primary HT, which can be overt or subclinical and has an approximate incidence rate of 20% to 40% [8]. This occurs because the radiation may affect the thyroid gland, which is located in the neck, and disrupt its normal function. This can lead to an underactive thyroid (HT) or other thyroid-related issues [9]. Management of radiation-induced thyroid dysfunction may involve thyroid hormone replacement therapy to maintain normal thyroid function and prevent symptoms associated with thyroid hormone deficiency [10].

Radiation exposure can have detrimental effects on the thyroid gland, leading to a spectrum of dysfunctions. Overt or clinical primary HT is defined as TSH concentrations above the reference range and free thyroxine concentrations below the reference range [11]. Mild or subclinical HT, which is commonly regarded as a sign of early thyroid failure, is defined by TSH concentrations above the reference range and free thyroxine concentrations within the normal range [11]. Central HT which is defined as HT due to insufficient stimulation by TSH of

an otherwise normal thyroid gland [12], Subclinical hyperthyroidism, which is characterised by circulating TSH levels below the reference range and normal serum thyroid hormone levels [13], Central hyperthyroidism which is a rare condition in which thyrotoxicosis results from primary overproduction of TSH by the pituitary gland with subsequent thyroid enlargement and hyperfunction [14].

The thyroid gland can be damaged during RCT, and this damage can manifest in various ways, including vascular damage, parenchymal (functional tissue) cell damage, and autoimmune reactions. The effects on thyroid function can vary from patient to patient [5]. The present study uniquely investigates the effects of RCT on thyroid function in HNC patients, emphasising the need for regular thyroid monitoring and early intervention to manage thyroid dysfunction.

MATERIALS AND METHODS

The present study was a retrospective study conducted in Department of Biochemistry at Medical College and SSG hospital, Baroda, Gujarat, India. Data of patients were collected from Radiology Department from period of January 2016 to April 2017.

Inclusion criteria: Only patients with complete data for six months and who were euthyroid prior to RCT were included.

Exclusion criteria: Patients with other cancers and those who did not complete the full RCT course were excluded (n=66).

Study Procedure

A total of 59 patients data were available and assessed at four stages based on the duration of RCT the subject received:

- Before RCT: Subjects assessed prior to initiating RCT.
- After 1 month of RCT: Subjects evaluated one month after starting RCT.
- After 3 months of RCT: Subjects assessed three months after starting RCT.
- After 6 months of RCT: Subjects evaluated six months after starting RCT.

The samples were analysed for serum TSH (0.5-5 µlU/mL), serum T3 (0.8-2.1 ng/mL), and serum T4 (5-12 µg/dL) by Enzyme-linked Immunosorbent Assay (ELISA) method, on the Microlab ELISA washer and Alere ELISA reader [15-17].

20 (34%), Ca. Buccal Mucosa 15 (26%), Ca. Larynx Pharynx 8 (13%), Ca Gingivobucccal 3 (6%), Ca Pyriform fossa 3 (6%). Furthermore, only discovered 2 (3%) subjects in each of the following: Ca Alveolous, Ca Lip, Ca Tonsil, Ca Vocal Cord, and Ca Vallecula.

The average age of participants was 51.7±2.4 years. The patient's demographics and gender distribution and study participants include more male patients compared to female subjects has been depicted in [Table/Fig-1].

Gender	Number of patients n (%)	Age (Mean±SD) (year)
Male	46 (78%)	52.1±2.5
Female	13 (22%)	50.5±1.33
Total	59 (100%)	51.7±2.4

[Table/Fig-1]: Demographics of subjects.
n: number of subjects

The mean thyroid levels of patients. Initially, patients were euthyroid before treatment began, but over a period of six months, they gradually developed HT has been depicted in [Table/Fig-2] [15-17].

Parameters	Reference range	Before starting RCT	After 1 month of RCT	After 3 months of RCT	After 6 months of RCT
Serum T3 (ng/mL) [16]	0.8-2.1	1.2±0.4	1.6±0.5	1.1±0.6	0.7±0.4
Serum T4 (µg/dL) [17]	5-12	9±2	11±3	8±2	5±1
Serum TSH (µlU/mL) [15]	0.5-5	2.4±1.9	1.9±2	3.2±2.2	7.5±7.1

[Table/Fig-2]: Mean and SD of thyroid levels [15-17].
T3: Triiodothyronine, T4: Thyroxine, TSH: Thyroid stimulating hormone

The level of T3 and T4 significantly decreased after six months following RCT (p=0.0001 and p<0.0001), respectively has been depicted in [Table/Fig-3]. Whereas [Table/Fig-4] shows the level of TSH level increased dramatically after three months of RCT (p<0.0001). These findings suggest that the RCT can cause the HT over period.

The thyroid status of subjects for period of six months has been depicted in [Table/Fig-5]. The percentage of individuals with normal thyroid function (euthyroidism) decreased from 100% before the RCT

Effect of RCT on serum T3 and T4		Before starting RCT		After 1 month of RCT		After 3 months of RCT		After 6 months of RCT	
		Serum T3	Serum T4	Serum T3	Serum T4	Serum T3	Serum T4	Serum T3	Serum T4
Before starting RCT	SerumT3	-		0.0084*	-	1	-	0.0001*	-
	Serum T4			-	0.0044*	-	0.0173*	-	< 0.0001†
After 1 month of RCT	SerumT3	0.0084*	-	-		0.0097*	-	< 0.0001†	-
	Serum T4	-	0.0044*			-	< 0.0001†	-	< 0.0001†
After 3 months of RCT	SerumT3	1	-	0.0097*	-	-		0.0004*	-
	Serum T4	-	0.0173*	-	< 0.0001†			-	< 0.0001†
After 6 months of RCT	SerumT3	0.0001*	-	< 0.0001†	-	0.0004*	-	-	
	Serum T4	-	< 0.0001†	-	< 0.0001†	-	< 0.0001†		

[Table/Fig-3]: ANOVA test results for serum T3 and T4.
*p< 0.05 considered significant, †p< 0.001 considered highly significant
T3: Triiodothyronine; T4: Thyroxine; TSH: Thyroid stimulating hormone; RCT: Radio Chemotherapy

STATISTICAL ANALYSIS

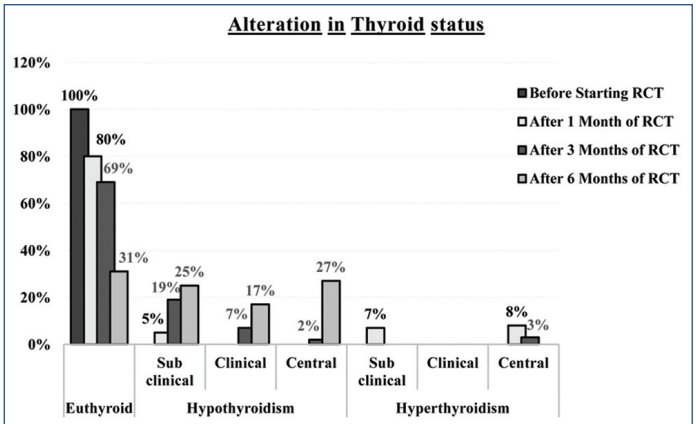
Data was entered and analysed using the software MedCalc® version 20.106. Continuous variables were summarised using standard deviations and mean. Groups were compared using the ANOVA test. A p-value of <0.05 was considered significant.

RESULTS

In present study, includes 59 subjects out of these 46 (78%) were male and 13 (22%) of subjects were female. The primary site of HNC in those subjects was Cancer of (Ca.) base of tongue

Effect of RCT on serum TSH	Before starting RCT	After 1 month of RCT	After 3 months of RCT	After 6 months of RCT
Before starting RCT	—	0.1803	0.0159*	0.0003*
After 1 month of RCT	0.1803	—	< 0.0001†	< 0.0001†
After 3 months of RCT	0.0159*	<0.0001†	—	0.0009*
After 6 months of RCT	0.0003†	<0.0001†	0.0009*	—

[Table/Fig-4]: ANOVA test results for serum TSH.
*p<0.05 considered significant, †p<0.001 considered highly significant
T3: Triiodothyronine; T4: Thyroxine; TSH: Thyroid stimulating hormone; RCT: Radio Chemotherapy



[Table/Fig-5]: Alteration in thyroid status.

to 31% after six months. The incidence of both subclinical and clinical HT increased over time. It suggests that the RCT had a significant impact on thyroid function, leading to a decrease in euthyroidism and an increase in HT.

It can be seen from [Table/Fig-1,5] that 59 (100%) of subjects were euthyroid (normal Thyroid hormone levels) before the starting of RCT. After one month of treatment out of 59 subjects, 47 (80%) of subjects were euthyroid, 3 (5%) of subjects developed subclinical HT, 4 (7%) developed subclinical hyperthyroidism and 5 (8%) of subjects developed central hyperthyroidism

After three months of RCT out of 59 subjects who were undergoing RCT, 41 (69%) were euthyroid, 11 (19%) of subjects developed subclinical HT, 4 (7%), and 1 (2%) developed clinical and central HT respectively, whereas 2 (3%) developed central hyperthyroidism. Out of 59 subjects who were undergoing RCT for six months of RCT only 18 (31%) remain euthyroid, 15 (25%) of subjects developed subclinical HT, 10 (17%) developed clinical 16 (27%) of subjects developed central HT and none of the subjects developed hyperthyroidism.

DISCUSSION

The RCT for HNC is known to have significant impacts on thyroid function, with HT being a common late side-effect [18]. This is corroborated by findings that demonstrate a significant decline in serum T3 and T4 levels, coupled with a substantial increase in TSH levels, particularly after six months of RCT. This aligns with previous studies that have reported an incidence of Radiotherapy-Induced Hypothyroidism (RIHT) ranging from 20% to 50% [19-21].

While present study observed an initial increase in T3 and T4 levels after one month of RCT, followed by a subsequent decline, this transient hyperthyroid phase was not consistently reported in previous studies. Further research is warranted to investigate the underlying mechanisms and clinical significance of this observation.

Uddin N et al., on 100 patients with neck Squamous Cell Carcinoma (SCC) stage I to stage III. Out of them, 25 patients (27.8%) developed subclinical HT [22]. While Randhawa AS et al., on 45 patients after three months of treatment, six patients developed HT (4 subclinical and 2 clinical). After six months 14 patients develop HT (10 subclinical and 4 clinical) [23]. A key finding in present study was the significant increase in serum TSH levels after six months of RCT, with a mean value of 7.5±7.1 mIU/mL [Table/Fig-2]. This substantial elevation strongly suggests the development of HT in a significant proportion of patients. This finding highlights the importance of close and vigilant thyroid function monitoring in HNC patients undergoing RCT. In present study with 6-months follow-up in 59 patients, showed a higher incidence of HT months [Table/Fig-5], affecting 41 (69%) {including 15 (25%) subclinical, 10 (17%) clinical, and 16 (27%) developed central}. This suggests that the impact of RCT on thyroid function in present cohort might be more as compared to some previous studies.

The iatrogenic cause of HT is known to be radiation, however RIHT is still underdiagnosed due to overlooked symptoms and a lack of follow-up consensus In a study on 45 patients of HNC on RCT, over a period of nine months, Srikantia N et al., reported an incidence of 14 (31.1%) clinical HT and 5 (11.1%) subclinical HT [24]. Tell R et al., in their study on 264 patients over the period of 19 months, reported that 6% of patients developed clinical and 22% developed sub-clinical HT [25].

Regular thyroid monitoring is crucial for HNC patients undergoing RCT. Early detection of thyroid dysfunction allows for timely intervention. Improved patient management and reduced risk of complications. Consider individual factors and radiation dose when planning follow-up. Early detection and management can significantly improve patient well-being.

Further study on effect of Radiochemotherapy on thyroid function is required to be carried on a larger no of patients along with its correlation with radiation dose, site of cancer and other treatment modalities. Longitudinal studies require to track long-term effects. Comparative studies require to identify optimal RCT regimens.

Limitation(s)

The present study was retrospective, which may have limitations in terms of data collection and analysis. A larger sample size and prospective design would be beneficial for further investigating the impact of RCT on thyroid function.

CONCLUSION(S)

Following definitive radiation, HT is a common late side-effect. From present study, authors concluded that treatment of HNC with RCT may affect thyroid functions. In these patients, there is a tendency to develop hyperthyroidism initially after one month of RCT, but later on, HT develops. Hence, it is advisable to test thyroid profile on regular follow-up to enable early diagnosis and treatment of any thyroid dysfunction if develop after RCT.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jul 22, 2024
- Manual Googling: Feb 15, 2025
- iThenticate Software: Feb 18, 2025 (10%)

ETYMOLOGY: Author Origin

EMENDATIONS: 8

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? No
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Jul 21, 2024**
Date of Peer Review: **Oct 08, 2024**
Date of Acceptance: **Feb 20, 2025**
Date of Publishing: **Jun 01, 2025**