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EARLY THYROID FUNCTION ALTERATIONS AFTER EXTERNAL BEAM RADIATION THERAPY – A PROSPECTIVE, OBSERVATIONAL STUDY

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ABSTRACT **Background:** External beam radiation therapy (EBRT) is commonly used in the management of head and neck squamous cell carcinoma (HNSCC) and affects the thyroid gland. We conducted this study to evaluate the spectrum of early thyroid dysfunction following EBRT.

Methods: We included 40 patients (any age, HNSCC requiring EBRT) in this prospective, observational study. All patients underwent thyroid function tests before and after EBRT at serial intervals of 1, 3 and 6 months. Descriptive statistics were used for presenting the data.

Results: The study population (37M, 3F) had a mean age of 57 ± 3.3 yrs. The mean TSH level fell initially and rose again at 3 and 6 months (mean TSH was 1.55, 1.34, 1.71 and 2.4 mU/L at 0, 1, 3 and 6 months respectively). Free thyroid hormones did not change significantly during the observation period. Four patients had low TSH at 1 month, which persisted in only one patient during the follow up at 6 months. Two patients developed hypothyroidism and none of the patients were symptomatic for thyroid dysfunction.

Conclusion: Transient thyroid alterations have been observed in patients after EBRT and the disease often remains silent. Frequent assessment for thyroid dysfunction should be done in patients undergoing EBRT for HNSCC.

KEYWORDS : Hyperthyroidism; Hypothyroidism; Thyroiditis; Radiotherapy

INTRODUCTION:

Head and neck cancers are a significant problem in India and constitute approximately one-third of all cancers. [1] The commonest site of malignancy is oral cavity and other sites include larynx, hypopharynx, oropharynx and nasopharynx. [2] The treatment of head and neck squamous cell carcinoma (HNSCC) often involves radiotherapy (RT), either in the adjuvant setting or as the definitive treatment modality. The RT fields include the site of the primary disease as well as the cervical lymph nodes. Thyroid gland invariably receives incidental radiation, by virtue of its location in the neck and manifests a variety of radiation toxicities. Primary hypothyroidism is the commonest complication due to the therapeutic external beam radiation therapy (EBRT). It is produced after therapeutic doses ranging from 30-70Gy. [3] Post RT thyrotoxicosis has also been described and occurs more acutely than hypothyroidism. [4] Thyrotoxicosis is due to the release of the preformed hormones into circulation leading to a transient suppression of Thyroid Stimulating Hormone (TSH) due to negative feedback mechanisms. [5]

The symptoms of thyroid dysfunction are nonspecific and are often masked due to the underlying cancer and general debility. The patients with HNSCC have symptoms like weight loss, palpitations, poor oral intake and easy fatigability. The clinical features are compounded in patients receiving concurrent chemotherapy. Due to the general poor intake and toxicities of treatment the performance status of most patients worsens near the end of EBRT. Thyroid dysfunction is often overlooked in such a scenario during the management of such patients. Previous studies have focused on the long-term thyroid changes after EBRT rather than the actual short-term fluctuations. Hence, we conducted this study to observe the changes in the thyroid functions in patients undergoing EBRT for HNSCC.

MATERIALS AND METHODS:

Study population: We conducted this prospective, observational study in a tertiary level, armed forces teaching hospital. We included all patients with HNSCC reporting to our department for the EBRT between October 2017 and September 2018. We included patients with localized or locally advanced HNSCC receiving at least 60 Gy of RT to the face and neck, either as definitive treatment and as adjuvant treatment, with or without chemotherapy. We excluded patients with known goitre or thyroid disorder, past history of radioiodine therapy, received neck radiation for any other reasons earlier and use of thyroid hormone preparation in the past. The institutional ethics committee approved the study protocol and all the patients provided informed written consent for the participation in this study.

Study measures: A detailed clinical history was taken to include the demographic details, family history of thyroid disorders and symptoms to suggest thyroid dysfunction. Examination was conducted with special focus on the head and neck area for delineating the radiation field. The presence or absence of the goitre was assessed by an endocrinologist as per the World Health Organization (WHO) grading. A fasting serum sample was taken from all the participants prior to the EBRT for the estimation of the thyroid panel including thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4) and thyroid peroxidase (TPO) antibody.

All patients received EBRT to face and neck region with a dose ranging from 60Gy to 70Gy @ 200cGy per fraction over 6-8 weeks. The planning was done using a 2-D technique and as a general rule, patients received five fractions of RT in a week with a gap of two days between two consecutive weeks. Spine sparing was done as per the institutional protocol and involved nodes were treated with electron boost by Linear Accelerator up-to 70 Gy. Patients advised for concurrent chemotherapy were given Injection Cisplatin in either weekly ($40mg/m^2$ dose for 6 weeks) or tri-weekly ($100 mg/m^2$ for two doses) regimes. The thyroid hormone panel (FT3 – Free Tri-iodothyronine, FT4 – Free Thyroxine and TSH – Thyroid stimulating hormone) was repeated at 1, 3 and 6 months after initiation of EBRT. Thyroid hormones were estimated using the electro-chemiluminescence technique and the intra / inter-assay variation in our laboratory was less than 6% for all the tests.

Study definitions: Hypothyroidism was diagnosed in the presence of low FT3 and FT4 with either raised TSH (primary) or normal / low TSH (Central). Thyrotoxicosis was diagnosed with elevated FT3 and

FT4 with suppressed TSH. Goitre was evaluated using the WHO definition. TPO positivity was indicated by the antibody titre >16 IU/mL

Statistical analysis: Descriptive statistics like mean ± standard deviation, frequency and percentages were used for presenting the study data. Follow up data were analyzed using the repeated measures ANOVA test and p-value of less than 0.05 was considered significant in all the tests.

RESULTS:

The study participants (37 males and three females) had a mean age of 57 (3.3) yr and mean duration of disease symptoms for two (3.2) months. The two common sites of HNSCC were oropharynx (16 out of 40) and oral cavity (11 out of 40). Other sites of involvement include the hypopharynx (six) and supraglottis (three). Majority of the patients (30 / 40) received definite RT, whereas the remaining ten received adjuvant RT. A total of 26 patients received concurrent chemotherapy of either regime along with RT. TPO antibody was positive in six out of 40 patients at the baseline. The thyroid hormone profile at baseline and serially is given in table 1. Briefly, the TSH level reduced at 1 month and increased thereafter within the normal range as shown in figure 1. The pattern of TSH change was same in all patients irrespective of the use of chemotherapy as shown in figure 2. The observed changes in the free thyroid hormones was not significant during the course after EBRT. Four patients had suppressed TSH at 1 month, which returned to normal in 3 patients at the end of 6 months observation. Hence, only one patient was considered to have radiation thyroiditis with thyrotoxicosis. Two patients developed hypothyroidism, the first patient being at the first month itself. The pattern of thyroid hormone alteration was similar irrespective of the age, gender and underlying thyroid autoimmunity (Data not shown).

Table 1. Thyroid hormone changes in the study participants

Parameter	Baseline	1st month	3rd month	6th month	p-value
Free T3	2.87 (0.67)*	2.92 (0.59)	3.37 (3.25)	2.99 (0.62)	0.5130
Free T4	1.30 (0.24)	1.37 (0.22)	1.23 (0.3)	1.35 (0.48)	0.6224
TSH	1.55 (1.04)	1.38 (1.12)	3.81 (13.2)	2.4 (1.2)	0.3092

*Mean (SD)

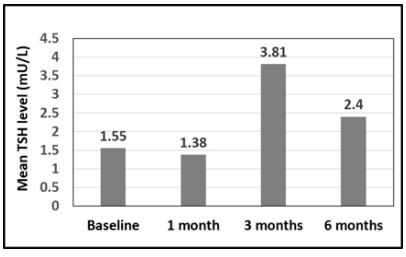

Figure 1: Mean TSH of all the patients

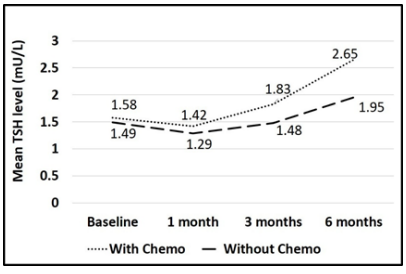

Figure 2. Mean TSH in patients with and without concurrent chemotherapy

DISCUSSION:

In this prospective, observational study albeit for a limited duration, we have shown that the thyroid hormones fluctuate in a narrow range after EBRT. The most significant abnormality was the suppression of the TSH in the 1st month with no significant changes in the levels of the free thyroid hormones. In our study, only a few patients with abnormal TSH level showed corresponding change in the FT3 and FT4 levels. The FT3 and FT4 levels changed only after a marked change in the TSH level. Therefore, the FT3 and FT4 levels was less sensitive than TSH for both kinds of thyroid abnormality.

Hypothyroidism was seen in two out of 40 patients, thereby giving a prevalence rate of 5%. Previous studies have shown that post RT hypothyroidism was seen in 20% to 30% of patients. [6-14] One of the patients developed hypothyroidism as early as at the end of 1 month and the other patient developed after 3 months. Studies done earlier have also shown mildly raised TSH by 6 months but rise by 4 weeks was unexpectedly early. [15,16] Post RT thyrotoxicosis persisting up to 6 months was seen in only one patient. Thyroiditis after RT is generally self-limiting within 3 – 4 months and persists rarely beyond 6 months. Post RT thyroiditis was seen in four out of 40 patients giving a prevalence rate of 10%. These results were similar to other studies done on the subject. [17,18]

Our data showed a high prevalence of males over females (11:1). The overall male: female ratio of HNSCC in Indian urban and rural population is 2:1 and 5:1 respectively. [19] The male preponderance in our study could be attributed by the fact that, our hospital being the tertiary care referral centre for the armed forces attract a higher percentage of male patients. Few studies have shown that female gender is a risk factor for development of post RT hypothyroidism. [20,21]

However, we are unable to compare the same due to small proportion of females in our study population. Our data showed that the observed variation in the thyroid function was irrespective of the use of chemotherapeutic agent (Cisplatin). The two different regimes of chemotherapy and the small number of events preclude us to make any meaningful observation about the same.

The presence of thyroid autoimmunity predisposes the person to thyroid dysfunction. TPO positivity increases the risk of developing hypothyroidism in comparison to the general population. In our study, the antibody positivity did not show any significant effect on the thyroid function. This could be explained by the altered immunity in the HNSCC patients, modulation of the autoimmunity by the RT and also the limited follow up duration. Z Lin et al [22] had done a longitudinal study on the correlations of thyroid antibody and thyroid hormone levels after radiotherapy in patients with nasopharyngeal carcinoma. The anti-TPO and anti-TG of the hypo group were higher than the normal group. But this correlation was made at 18 months post RT, which is much later than the final thyroid hormone profile in our study. The strengths of our study include the prospective design and exclusion of the confounding factors that could affect the thyroid hormone changes. The limitations of our study are small sample size, short follow up duration and the data being from the single center may not be applicable for other general population.

To conclude, our study suggests that TSH change is the most common thyroid hormone alteration in the acute phase after the EBRT. Permanent thyroid dysfunction was observed in a minority of patients and most of them are asymptomatic for thyroid disease. Further long-term studies with a greater number of patients are required to confirm the findings observed in our study.

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