Assessment of Thyroid Dysfunction in Patients Irradiated for Head and Neck Malignancies

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ABSTRACT

BACKGROUND
This study aims to assess the changes in serum TSH (Thyroid-Stimulating Hormone) in subjects with head & neck carcinoma treated with External Beam Radio-Therapy (EBRT) and study the usefulness of the serum TSH test to identify patients who develop early hypothyroidism in these subjects.

METHODS
This study involved assessing serum TSH in 50 patients diagnosed with biopsy-proven squamous cell carcinoma in the head & neck region treated with external beam radiotherapy (EBRT). The study was designed as a prospective non interventional observational study. All patients underwent serum TSH test before the start of the radiation, at 2 months after the radiation and at 6 months after the radiation. All documented serum TSH levels were taken up for analysis.

RESULTS
Patient population was characterized by the distribution of patients in subsite of oral cavity in 18 (36 %) patients, hypopharynx in 11 (22 %) patients, larynx in 11 (22 %) patients, oropharynx in 9 (18 %) patients, and nasopharynx in 1 (2 %) patient. 12 (24 %) subjects were in Stage II, Stage III in 34 (68 %) subjects, and Stage IV in 4 (8 %) subjects. Mean TSH before radiotherapy was 1.93 ± 0.72 IU / mL. The mean TSH after 2 months of radiotherapy was 2.25 ± 0.97 IU / mL. The mean value after 6 months was 2.5 ± 1.3 IU / mL. The difference between the mean TSH values of 2 months and 6 months compared to baseline TSH is statistically significant ($p < 0.0001$ between 2 months and baseline and $p < 0.0001$ between 6 months and baseline). There was a 17 % increase in the TSH levels after 2 months of radiotherapy and a 30 % increase after 6 months of radiotherapy.

CONCLUSIONS
There is an increase in the serum TSH values both after 2 months and after 6 months of radiation and also may help in identifying patients with impending hypothyroidism at the early stage.

KEYWORDS
Radiotherapy, TSH, Thyroid, Hypothyroidism, Head and Neck Cancer

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BACKGROUND

Based on the findings of our research, assessment of changes in TSH serum in subjects with head & neck cancers treated with external beam radiotherapy may result in an increase in TSH serum values after 2 months and 6 months of radiation and may also help to distinguish patients with imminent early hypothyroidism.[1,2] The main risk factors for head and squamous cell carcinoma of neck in the Western population are cigarette-smoking and alcohol consumption whereas the use of smokeless tobacco and areca nut are the most common risk factors in Southeast Asia. Human Papilloma Virus (HPV) is an important causative factor for carcinoma of squamous cell in the head and neck. The total prevalence of HPV in HNSCC (Head and Neck Squamous Cell Carcinoma) is approximately 50 per cent with the highest prevalence of tonsil and tongue base cancers. The two main treatment modalities for headache and neck cancer are surgery and radiotherapy with or without chemotherapy.[3] The goal of radiation therapy is to provide accurately calculated dose of dose to a given tumour volume with as minimal damage as possible to the healthy tissue surrounding it, resulting in tumour eradication, high quality of life and survival prolongation.[4]

In EBRT to malignancies of the head and neck, the area of radiation to the target volume typically includes the thyroid gland that causes its damage. Iatrogenic causes like external neck irradiation may cause primary hypothyroidism for head and neck malignancies. The high doses to the thyroid gland can contribute to its malfunction when treating patients with neck radiation in head and neck malignancies.[5]

Even the mechanism of hypothyroidism due to EBRT is incompletely comprehended. This may be due to direct follicular suppression or destruction of thyroid gland vascular damage, or cell division or immunologically mediated thyroid gland damage, or a number of combinations of factors. Since adult in vivo thyroid cells are not expected to have a high turnover rate and are well differentiated, it has been proposed that they can undergo radiation-induced apoptosis, which differs from patient to patient.

METHODS

Prospective non interventional observational clinical study was conducted at a tertiary care oncology hospital. The patient and attendant were explained regarding the use of doing serum TSH, baseline and on follow-up, and consent taken for the same. 50 Patients proven with squamous cell carcinoma of head and neck and receiving radiotherapy were included in the study. This study was commenced after obtaining clearance from the hospital Ethics and Scientific Committee.

This study involved the assessment of serum TSH in 50 patients who were diagnosed with biopsy proven squamous cell carcinoma of head and neck region between April 2015 and May 2016 at Apollo Speciality Hospitals, Chennai. The study was designed as a prospective observational study. All the patients will undergo serum TSH test before the start of the radiation, at 2 months after the radiation and at 6 months after the radiation.

All patients were evaluated by a team comprising of a radiation oncologist and medical oncologist. Staging work up comprised of clinical examination, routine blood tests comprising of liver function test, renal function tests, complete blood count and imaging studies like chest x ray and a CT scan of head and neck.

After staging work up was completed, patients were subjected to radiation with concurrent chemotherapy. Radiation technique and frequency of chemotherapy (weekly) was planned for all the patients.

After obtaining the informed consent, patients were taken up for radiotherapy preparation. The demographic data of the patients was collected at the time of preparation.

All patients were properly immobilized with a suitable neck rest and Aquaplast mask. Shoulder retractor was used when necessary.

After proper immobilization in treatment position technique – Plain CT images of head and neck were taken from base of skull to clavicle with a simulator CT machine. The acquired axial images were transferred to the treatment planning system (Oncentra Treatment planning system version 4.1) in DICOM format. These images received in the treatment planning system were first registered and re-constructed for contouring.

Figure 1. Patient with Aquaplast Mask

The primary and node volume with adequate margins that is Clinical Target Volume (CTV) and Gross Tumour Volume (GTV) were contoured along with Organs at Risk (OAR) in the axial plane. The thyroid gland is contoured but not as an organ at risk and no dose constraints were given to the thyroid gland and the therapeutic dose to the neck was not compromised. All the contours were verified by the radiation oncology consultant before treatment planning.

The treatment planning was done by the qualified medical physicist using Oncentra (version 4.1) treatment planning system. Each plan was evaluated by the radiation oncology consultant. On approval of the plan, treatments were delivered on linear accelerator with 6 MV photons.

Patients were treated with Intensity Modulated Radiotherapy (IMRT) with concurrent Cisplatin based chemotherapy as per protocol. 66 Gy / 33 # / 6 - 7 weeks, 5 days / week; single fraction / day. Energy: 6 MV photons.

Chemotherapy is by Cisplatin dose depending on body surface area of the patient. Inj. Cisplatin 40 mg / m^2 IV in 500 mL of normal saline over 1 hour. Weekly during radiation therapy up to maximum six cycles.

Follow-up schedule: Serum TSH baseline before the start of radiotherapy. Serum TSH after 2 months of completion of the radiotherapy. 3. Serum TSH after 6 months of the completion of radiotherapy.

TSH estimation was done using immunoradiometric assay. The normal values used for the study was TSH – 0.5 - 5.1 mIU / L.

Inclusion Criteria

Patients between the ages of 18 - 80 years with histologically confirmed head & neck squamous cell carcinoma who were expected to receive external beam radiation to both the first site and the neck and whose radiation field will include the thyroid gland.

Exclusion Criteria

1. Patients of thyroid metastasis, positive thyroid disease history or thyroid surgery.
2. Due to their predicted limited survival, patients with T4 larynx tumours that invade the thyroid gland or N3 neck nodes or distant metastasis at present were not included in the analysis.
3. Patients who have one or more nodules in the thyroid gland, as well as those who have undergone laryngectomy before radiation, while they may presently be euthyroid. Since the aim of the study is to see the changes in serum TSH values post radiotherapy, the expected change in mean serum TSH values from base to 6 months post radiation being 0.6 mIU / L. With two tailed distribution, effect size of 0.42, difference in serum TSH from base to 6 months post RT of 0.6, the required sample size is 45 cases. By considering 10 % drop out the required sample size is 50 cases. The sample size is calculated based on the software G* power 3.1.9.2. The formula used for the sample size calculation: $n = (z_{\alpha} / 2)^2 \sigma^2 / E^2$ Where; $z_{\alpha} / 2$ is standard normal variate value (1.96) σ is the standard deviation (1.5 mIU / L) E is the margin of error (0.4).

Statistical Analysis

Using Shapiro Wilks' test, all the continuous variables were tested for normality. If the variables are distributed normally they will be represented as mean ± Standard Deviation (SD), otherwise median (interquartile range). Both categorical variables are either expressed as percentage or proportion. Continuous variables are compared by paired 't' test. Chi square test or Fisher's exact test can allow comparison of categorical variables. The data entry is performed in the spread sheet of MS-excel. All p values < 0.05 are deemed statistically important. * SPSS version 16.0 will do the data processing.

RESULTS

50 patients were analysed. The Demographic data of the patients were as follows. Of the 50 patients, 80 % were male and 20 % were female.

Gender	Frequency	Percentage (%)
F	10	20
M	40	80
Total	**50**	**100**
Age in years		
< = 40	6	12
41 - 50	14	28
51 - 60	20	40
61 - 70	6	12
> 70	4	8
Total	**50**	**100**
Subsite		
Hypopharynx (HPX)	11	22
Larynx (LRX)	11	22
Nasopharynx (NPX)	1	2
Oral Cavity (OC)	18	36
Oropharynx (OPX)	9	18
Chemotherapy		
Yes	47	94
No	3	6
Stages	Frequency	Percentage (%)
II (T2N0M0)	12	24
III (T2N1M0)	10	20
III (T3N0M0)	13	26
III (T3N1M0)	11	22
IVA (T2N2aM0)	1	2
IVA (T3N2aM0)	2	4
IVA (T4aN1M0)	1	2
Grand Total	**50**	**100**

Table 1. Demographic Distribution

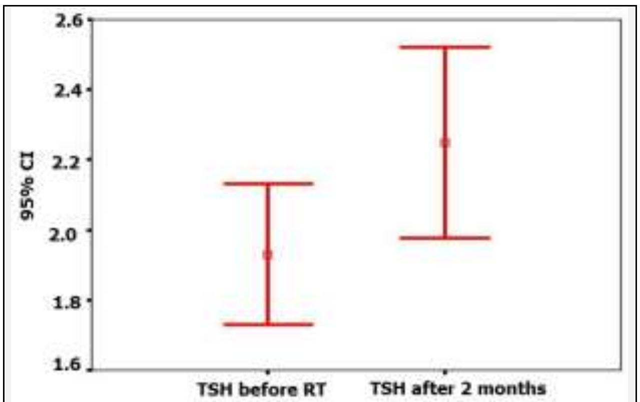

Figure 2. Error Bar Showing the Difference in TSH at 2 Months

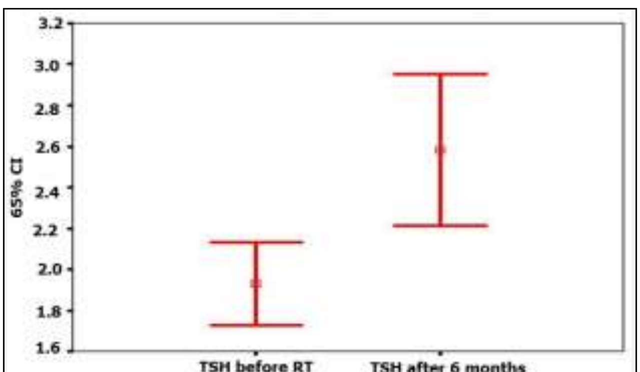

Figure 3. Error Bar Showing the Difference in TSH Post 6 Months RT

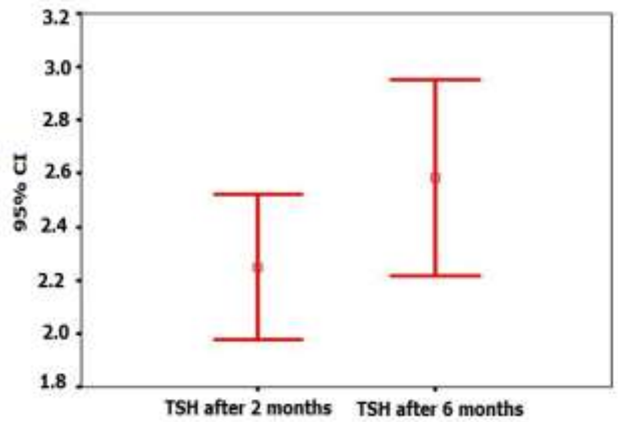

Figure 4. Error Bar Showing the Difference in TSH Post 2 Months vs. Post 6 Months

Time Points / TSH Levels	0-1 mIU/L	1.01-2 mIU/L	2.01-3 mIU/L	3.01-4 mIU/L	4.01-5 mIU/L	> 5 mIU/L
Before RT	4	26	16	4	0	0
Post 2 months RT	1	23	19	3	4	0
Post 6 months RT	0	22	18	5	1	4

Table 2. Comparison of TSH Levels across Time Intervals

The mean TSH before radiotherapy was 1.93 ± 0.72 IU / mL. The mean TSH after 2 months of radiotherapy was 2.25 ± 0.97 IU / mL. The mean value after 6 months was 2.5 ± 1.3 IU / mL.

The difference between the mean TSH values of 2 months and 6 months compared to baseline TSH is statistically significant ($p < 0.0001$ between 2 months and baseline and $p < 0.0001$ between 6 months and baseline).

There was a 17 % increase in the TSH levels after 2 months of radiotherapy and a 30 % increase after 6 months of radiotherapy.

DISCUSSION

Subclinical (or mild) hypothyroidism is a state of normal free thyroid hormone levels and low thyroid stimulating hormone elevation; some patients may have minor symptoms. Despite these findings, the follow-up procedures for patients with head and neck malignancies also do not include testing for thyroid functions. In our study, we measured the baseline serum TSH before the start of the radiation and followed up after 2 months and 6 months of completion of the radiation. Alterio D, et al.[6] also evaluated thyroid function mainly by measuring serum TSH and reported 26 % incidence of hypothyroidism in their retrospective study. The increase in the mean serum TSH values was 18 % after 2 months and 36 % after 6 months of radiation. But the incidence of increase in serum TSH was only 8 % after 6 months post radiotherapy.

In comparison with the published literature, our study shows an elevation of TSH as early as 2 months post radiotherapy. Koc M, et al.,[7] had reported an incidence of 25.4 % in his cohort with subclinical hypothyroidism after a median of 3 months post radiation. Laway BA, et al.,[8] reported an incidence of 16.9 % in their prospective study of 59 patients studied for 2 years duration and reported 4.5 months as the mean time for development of hypothyroidism. Aimoni C, et al.[9] observed hypothyroidism after 1 year of radiotherapy in 4 out of 30 patients.

Garcia-Serra A, et al.[10] has suggested checking of thyroid function every 6 months after radiotherapy and also suggested replacement when the TSH was over 4.5 IU / mL. In our patients, 2 percent of the cohort had values above the aforementioned level after 2 months post radiotherapy and 10 percent had values above 4.5 IU / mL after 6 months post radiotherapy.

In their analysis, Arun Chougule, et al.[11] showed that the levels of serum T4 and T3 lowered after finishing with external beam radiotherapy and persisit so after 6 months of follow-up. However, levels of the Serum TSH did not differ significantly. In our study there is significant variation in the difference in the mean value of TSH at baseline and 6 months follow-up.

Cetinayak, et al.,[12] have studied serum TSH values in 33 patients who received radiotherapy alone in one group every 3 months after the radiation and observed the incidence of 12.2 % at the median follow-up of 36 months and recommended follow up every 3 - 6 months after radiation. Our study showed increase in serum TSH above the upper limit in 8 % of the cohort at the end of 6 months thus establishing that a short follow up as early as 6 months can identify changes in thyroid dysfunction.

In our study, the low occurrence of hypothyroidism with a short follow-up duration of 6 months warrants long-term follow-up to determine the patient's change in euthyroid status. In their report, Miller MC, et al.[13] reported that the onset of hypothyroidism can be as early as 4 weeks and as late as 5 or 10 years after completion of therapy. Ozawa H, et al.[14] in their 10-year long-term follow-up of 35 patients with head and neck cancer neck radiation, hypothyroidism was found of 13 out of 35 patients. Out of 35 patients 22 patients received radiation alone and the incidence was 32 % (7 out of 22 patients) and 13 patients underwent surgery followed by radiation and the incidence was 46 % (6 out of 13 patients).

Mercado, et al.[15] studied 143 patients with a median follow-up of 4.4 years, ranging from 1.5 to 9.2 years, and reported a projected incidence rate of hypothyroidism in 5 years Kaplan-Meier as 48 percent, and a projected incidence rate of 67 percent in 8 years. The median time to hypothyroidism development was 1.4 years, with a range of 0.3 - 7.2 years in their study.

Tell, et al.,[16] and Mercado, et al.,[15] recorded no impact on the function of the thyroid gland by age, gender and primary location. Koc M, et al.,[7] Posner, et al.,[17] and Sinrad, et al.[18] found no effect of combination chemotherapy on thyroid gland function for head and neck malignancies in patients irradiated to the neck. In our sample 47 patients received combined chemotherapy and only 3 received no chemotherapy. We could not do a study on the effect of chemotherapy on thyroid dysfunction, due to the limited number of patients who did not undergo chemotherapy.

CONCLUSIONS

Subjects with head & neck cancers served with external beam radiotherapy, based on the results of our study, may find an improvement in serum TSH values both after 2 months and after 6 months radiation. Evaluation of changes in serum TSH in patients with head and neck cancers treated with external beam radiotherapy can help identify patients with imminent hypothyroidism at an early stage, based on the results of our analysis.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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