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Assessment of radiation induced alteration in Thyroid Hormone Profile and influence of concomitant chemotherapy in Head and Neck Cancers

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Abstract

Aims And Objectives: To evaluate effect of radiotherapy induced alteration in Thyroid Hormone Profile and its correlation with concomitant chemotherapy in Head & Neck Cancers.

Material And Methods: This prospective observational study was carried out on the patients of head and neck carcinoma planned for definite or chemo radiation. Analysis of total 64 patients was done having age group of 30-75 years (51.7 years) treated in Group A with external beam radiotherapy (51.6%) and Group B with concurrent chemo-radiotherapy with cisplatin (48.4%). Pre-enrolment baseline thyroid function test (TFT) before radiotherapy must be normal and the patients were monitored for TFT on completion of radiotherapy treatment, at 1 month, at 3 months and at 6 months after treatment. Serum Thyroid stimulating hormone (S.TSH), Serum triiodothyronine (S.T3) and Serum thyroxine (S.T4) were tested by immunoassay. Patients were treated with radical radiotherapy doses of 66Gy/33# or 60 Gy/30# based on the tumor profile. The target volume included the thyroid gland, which received an average dose of 60 Gy in 30#. One group of patients received radiotherapy alone while other group of patients had received concurrent chemo radiation.

Results: Out of overall 64 patients, 46 (71.9%) were males and 18 (28.1%) were females. All patients received radiotherapy to the neck at a dose of ≥60Gy, 48.4% patients received concurrent chemotherapy and 3 patients underwent prior neck dissection. It was detected that Serum T3 and Serum T4 increased significantly after 1 month ($p<0.01$) and decreased significantly after 6 months of treatment ($p<0.01$) whereas, S.TSH increased significantly after 3 months ($p=0.015$) of treatment. 14 patients (21.88%) were found to have clinical hypothyroidism ($P < 0.01$). 30 (46.87%) patients were found to have subclinical hypothyroidism with a total 44 of 64 (68.75 %) patients developing radiation induced hypothyroidism. 29 of 44 patients with hypothyroidism were in the age group of 51 to 60 years. In the younger age group (30-50 years) patients, TSH shows a statistically significant ($P < 0.05$) increase in TSH values.

Conclusions: Even after a short follow-up, the incidence of thyroid dysfunction was approximately 68.75% patients of head and neck cancer treated with combined surgery and radiotherapy or radio-chemotherapy. Subclinical hypothyroidism was seen in the radiotherapy treated patients of head and neck cancer. The patients with age less than 50 years were found more prone to develop hypothyroidism. Pretreatment screening of thyroid profile and 3 monthly follow up can enable early diagnosis and treatment of any thyroid malfunction which can develop after radio-chemotherapy. Isolated chemotherapy has not affected the incidence of hypothyroidism significantly.

Keywords: Head and neck cancer, hypothyroidism, radiotherapy, subclinical hypothyroidism, Thyroid profile.

Introduction

Radiation therapy plays an important role in the management of head and neck malignancies, used either alone or in combination with chemotherapy. Apart from surgery, definitive radiotherapy/radio-chemotherapy is the main treatment strategy in early & locally advanced Head & Neck Cancers. Head and neck cancers rank fifth among all malignancies worldwide and the commonest malignancy among Indian males.(1) This is probably due to the increased intake of tobacco in various forms.

The thyroid gland is the largest pure endocrine gland situated in the anterior neck in front of the trachea and secretes two main thyroid hormones, triiodothyronine (T3) and thyroxine (T4), which are crucial in normal growth and development. Although the thyroid gland is considered to be relatively radio-resistant, Hiroshima and Nagasaki bombings and the Chernobyl accident events have shown hypothyroidism and various other sequelae including thyroid malignancies. This indicates the existence of dose-effect relationship.(2)

Majority of head and neck tumors are loco-regionally advanced at the time of diagnosis. Hence, thyroid gland comes into the radiotherapy treatment portals in most of the cases. This leads to radiation induced thyroid dysfunction.The dysfunctions ranged from thyroiditis, autoimmune thyroiditis, hypothyroidism, and thyroid tumors. Impact of radiotherapy on thyroid function was first reported in 1929.(3) The radiation-induced thyroid injury includes parenchymal cell damage, autoimmune reactions and vascular damage.

The irradiated volume of thyroid gland, total radiation dose and the extent of prior thyroid resection are the important factors associated with the risk of hypothyroidism. The most common clinical late effect of

thyroid gland irradiation in patients exposed to therapeutic doses to the neck is hypothyroidism. Primary hypothyroidism often develops as a result of radiotherapy to the cervical region in therapeutic doses (30-70 Gy) in patients with head and neck cancer. This effect may be clinically overt (clinical hypothyroidism) characterized by low free T4 and high thyroid stimulating hormone (TSH), or subclinical (biochemical or compensated hypothyroidism) with normal free T4 and high TSH. In the majority of cases, subclinical hypothyroidism evolves to clinical hypothyroidism.(4)

On literature search, it is seen that hypothyroidism after radiotherapy alone or in combination with surgery and/or chemotherapy for patients with head-neck cancers is reported between 17% and 51%.(5)(6)This prospective non randomized study allowed us to evaluate the incidence, extent, relationship of hypothyroidism, and thyroid- stimulating hormone (TSH) levels with malignancy- related outcomes.

Materials And Methods

This study was conducted in histo-pathologically proven head and neck cancer patients of any age, both the sexes with normal thyroid function receiving external beam radiotherapy to the whole neck on Tele-cobalt (Th-780C) from January 2016 to April 2018 and were planned to be treated with definitive radiotherapy/radio-chemotherapy. Patients with a thyroid disease or thyroid surgery, abnormal pretreatment thyroid function tests and any previous history of radiation therapy to thyroid were excluded from the study.

All Patients were evaluated as per standard protocol for Head & Neck Cancer patients who included history, general physical examination, loco-regional examination, endoscopy & biopsy from primary site for histopathological confirmation. This was followed by radiological investigations like chest X-ray, CT scan/MRI Head & neck region, dental evaluation/Orthopantomogram (OPGs), &whole body PET-CT whenever indicated. Baseline ECG/2D Echocardiography was done as per indication. Hematological investigations included CBC with platelet count, Renal and Liver function tests, Random/Fasting blood sugar tests and other specific tests if indicated.

Table: 1 Patient and disease characteristics (N=64)

Gender	Male	46 (71.9 %)
	Female	18 (28.1 %)
Age (Years)	Range	30 – 75
	Mean age ± (SD)	57.3 ± 11.4
Primary Tumor site	Ca Base of tongue	22 (34%)
	Ca Buccal Mucosa	16 (26%)
	Ca Larynx,Pharynx	8 (13%)
	Ca Gingivo-bucccal	4 (6%)
	Ca Pyriform fossa	4 (6%)
	Ca Vallecula	2 (3%)
	Ca Lip	2 (3%)
	Ca Tonsil	2 (3%)
	Ca Vocal Cord	2 (3%)
	Ca Alveolus	2 (3%)
Stage	I	6 (9.37 %)
	II	10 (15.63 %)
	III	30 (46.88 %)
	IV	18 (28.12 %)

SD - Standard Deviation

Ca – Carcinoma

Staging was done as per latest AJCC/UICC staging system for head & neck Cancer. Then patients, who were fit for definitive radiotherapy alone or radio-chemotherapy, were included in the study. External field radiotherapy was given by Theratron 780C (Cobalt tele-therapy machine). This 2D radiotherapy plan consisted

of parallel opposed lateral beam portals giving a total dose of 66 Gy in 33# (or 60Gy/30#) over 6.3 weeks (5 fractions per week) along with concurrent weekly injection of Cisplatin 40 mg/m^2 iv for 6 cycles. The patients intolerant to Cisplatin were given weekly injection of Carboplatin (AUC 2) for 6 cycles. Thyroid gland could not be spared or partially spared due to 2D treatment and it was irradiated in all the patients for at least first phase of 50-60 Gy before shrinking the fields.

Table: 2 Treatment Characteristics (N=64)

		Mode of treatment	
		Group A Radiotherapy (%)	Group B Radio-chemotherapy (%)
No of patients		33 (51.6%)	31 (48.4 %)
Radiation dose	60 Gy	25 (39.1 %)	24 (37.5 %)
	> 60 Gy	8 (12.5 %)	7 (10.9 %)
Age	< 50 years	9 (14.1 %)	8 (12.5 %)
	≥ 50 years	24 (37.5 %)	23 (35.9 %)

The thyroid profile was performed in NABL accredited Biochemistry laboratory and it was done before radio-chemotherapy, and then after 1, 3 and 6 months of completion of radio-chemotherapy. Normal laboratory reference values of triiodothyronine (T3), thyroxin (T4) and Thyroid stimulating hormone (TSH) were 0.8–2.1 ng/ml, 5–13 µg/dl and 0.4–5.5mIU/ml respectively. Mean and Standard deviation (SD) were calculated. Statistical analysis was done using ANOVA test. The p value *<0.05* was considered as statistically significant.

Result

In this prospective, nonrandomized clinical study of 64 patients, 46 (71.9 %) were males and 18 (28.1 %) were females and majority were in the age group of 30 to 75 years. Primarily in majority of the patients were carcinoma Base of Tongue (34 %) [Table: 1]. 48.4 % patients received concurrent chemotherapy and 51.6 % received radiotherapy alone. Only three patients underwent prior surgery in the form of neck dissection before radiotherapy. Patients who followed up regularly were only included in the study. Consequently, the occurrence of clinical and subclinical hypothyroidism is studied over a follow-up period of 6 months in this prospective nonrandomized study.

Overall total 64 patients, 33 patients underwent radiotherapy and 31 patients underwent chemo-radiotherapy. Among all these patients who were treated with radiation dose of ≥ 60 Gy [Table: 2],S.T3 and S.T4 increased significantly after 1 month ($p<0.01$) and decreased significantly after 3 months of treatment ($p<0.01$) whereas, S.TSH increased significantly after 3 months ($p=0.015$) of treatment [Table 3]. In 6 months follow up, 14 patients (21.88%) were found to have clinical hypothyroidism. This was strongly significant with a $P<0.001$. Thirty patients (46.87%) were found to have subclinical hypothyroidism. In total, 44 of 64 (68.75%) patients had radiation-induced hypothyroidism [Table 4].

After 6 months follow-up, total 21 of 44 patients who received concurrent radio-chemotherapy and 23 of 44 who received RT alone developed hypothyroidism, which showed no statistically significant difference between radiotherapy and chemo-radiotherapy groups ($P > 0.10$) [Table 5].

In this study, among the patients who developed hypothyroidism, 29 of 44 were in the age group of 51 to 60 years and among males, 31 (67.36%) of 46 developed clinical hypothyroidism and among females, 13 (72.22%) of 18 developed clinical hypothyroidism [Table 5]. In younger age group (30-50 years) patients, TSH shows statistically significant ($P < 0.05$) increase in TSH values. On the other hand, only three patients underwent prior neck dissection and of them, one developed clinical hypothyroidism. Overall the patients who developed hypothyroidism, either clinical or subclinical, were seen by the Endocrinologist and put on thyroid supplementation.

Table 3: Mean thyroid levels (N = 64)

Duration from RCT / Thyroid Profile	Before Starting RCT	After 1 Month of RCT	After 3 Months of RCT	After 6 Months of RCT	P Value (ANOVA Test)
T3 (0.8-2.1ng/ml)	1.2 ±0.4	1.6 ±0.5	1.1 ± 0.6	0.7 ± 0.4	< 0.001
T4 (5-13 µg/dl)	9 ± 2	11 ± 3	8 ± 2	5 ± 1	< 0.001
TSH (0.4-5.5 mIU / ml)	2.4 ±1.9	1.9 ±0.9	3.2 ± 2.2	7.5 ± 2.1	< 0.001

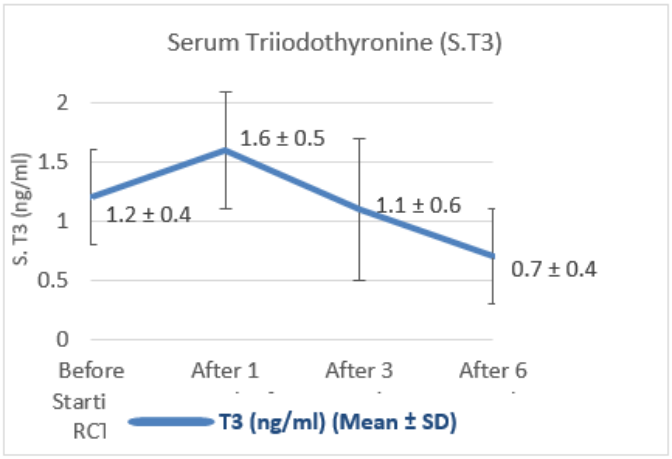

Fig. 1: Serum Triiodothyronine (S.T3) at different times of measurement

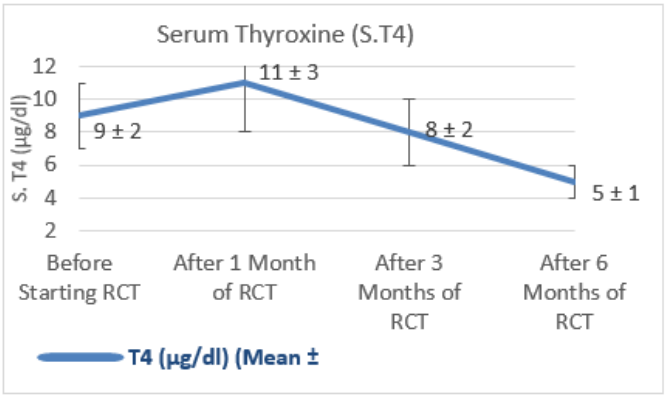

Fig. 2: Serum Thyroxine (S. T4) at different times of measurement

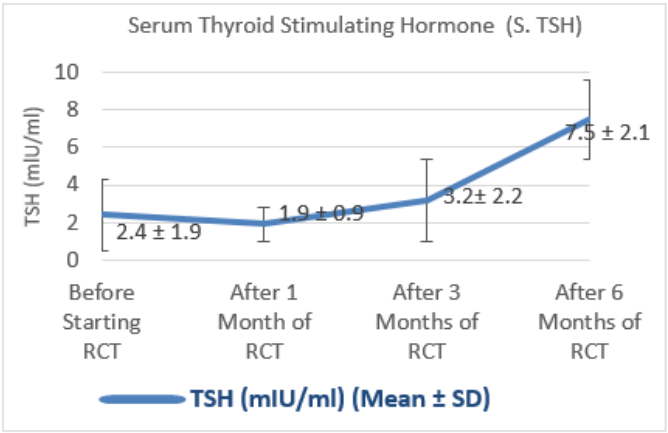

Fig. 3: Serum Thyroid Stimulating Hormone (S. TSH) at different times of measurement

Table 4: Status of hypothyroidism (N = 64)				
Outcome	Before RCT	After 1 Month of RCT	After 3 Months of RCT	After 6 Months of RCT
Normal	64 (100%)	62(96.88%)	50 (78.13 %)	20 (31.25 %)
Subclinical	0	2 (3.12 %)	12 (18.75 %)	30 (46.87 %)
Clinical	0	0	2 (3.12 %)	14 (21.88 %)

Table 5: Occurrence of hypothyroidism with chemotherapy					
Chemotherapy	No. of patients	No. of patients with hypothyroidism			Percentage
		Male	Female	Total	
Received	31	16	5	21	67.74
Not Received	33	15	8	23	69.70
Total	64	31	13	44	68.75

Discussion

Radiotherapy plays an important role in the management of head and neck cancers. The majority of new cases of invasive head and neck cancer need radiotherapy as a primary treatment, as an adjunct to surgery alone or in combination with chemotherapy or as palliation. Thyroid gland has an important role in keeping the metabolic activity in organized performing way.

A number of studies done in the 1960s have reported the development of hypothyroidism after radiotherapy for head and neck malignancies.(7)(8) In 1961, Felix *et al.*, first reported a case of hypothyroidism 6 years after treatment with external radiotherapy for laryngeal carcinoma.(7) Documented incidences of primary hypothyroidism after radiotherapy have varied from 3 to 47%. An incidence of 20 to 30% has been reported by most investigators.(9)

Alterio *et al.* mentioned that among different radiation-induced late effects, thyroid disorders are underestimated. Among thyroid disorders, primary hypothyroidism seems to be the most frequent late effect with an incidence of 20 to 30%.(10) Einhorn and Wikholm(11) followed 41 patients for more than 10 years after treatment for carcinoma of hypopharynx and larynx, 7.3% incidence of hypothyroidism was found.

Emami *et al.* reported different tolerance values of 8/5, 13/5, and 35/5 (incidence of clinical hypothyroidism in 8%, 13%, and 35% of patients at 5 years) at the level of 45, 60, and 70 Gy, respectively.(12)

Thyroid gland responds to radiation by acute rise in T3 and T4 level and decrease in TSH level. Even though values didn't cross normal range of particular hormone but it shows statistically significant change in level. Sharp rise and sharp fall in level of T3 and T4 hormone within limit signifies acute inflammatory changes. Patients with normal T4 levels and elevated TSH levels are considered to be in a "latent" or "compensated" hypothyroid state. This state is also known as subclinical hypothyroidism. Although TSH and T4 levels change inversely, it is recognized that there is not good correlation between the degree of elevation of TSH and reduction in serum T4 levels.(13) Normalization of T3 and T4 values towards the completion of treatment while increasing TSH value could not be explained by acute thyroiditis. But it explains hypofunction of thyroid post irradiation that results in higher level of TSH in comparison to TSH before irradiation to maintain T3 and T4 level. During this period of subclinical hypothyroidism the T4 levels are maintained by TSH levels.

In this study, S.T3 and S.T4 increased significantly after 1 month and decreased significantly upto 6 months of treatment whereas, S.TSH increased significantly after 3 months of treatment, which is well agreed with other studies.(14)(15)

The incidence of hypothyroidism in the present study was 68.75%. 14 patients (21.88%) were found to have clinical hypothyroidism and 30 (46.87%) patients were found to have subclinical hypothyroidism. Subclinical hypothyroidism occurs in 3%–8% of general population. It is more common in women and its incidence increases with age.(16) In the present study, total 13 out of 18 females developed hypothyroidism. Several studies show that the development of hypothyroidism has no correlation with sex or age of patients.(17)(18)It is expected that concurrent chemotherapy would sensitize the thyroid gland to radiation and will increase the incidence of hypothyroidism. But several studies (19)(20)found no effect of combination chemotherapy on thyroid gland function in patients with head and neck malignancies. In the present study, we used definite or chemo-radiation and the difference observed in the radiotherapy and chemo-radiotherapy group is also not statistically significant.

Conclusion

We can conclude that external irradiation in cancer, therapeutic doses can affect thyroid function in spite of shielding over neck. As hypothyroidism is a treatable condition, it can be detected early by well-defined pre and post irradiation investigation protocol for detection of hypothyroidism in head and neck cancer patients. Further study on effect of radio-chemotherapy on thyroid function can be carried out on a larger number of patients along with its correlation with radiation dose, site of cancer and other advanced treatment modalities.

Compliance with Ethical Standards: This study was conducted with due permission of Institutional Ethics Committee for Biomedical and Health Research.

Informed Consent: Informed consent was obtained from all individual participants included in this study.

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