Brief Communication

Incidence of primary hypothyroidism in patients exposed to therapeutic external beam radiation, where radiation portals include a part or whole of the thyroid gland

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ABSTRACT

Introduction: Hypothyroidism is a known consequence of external-beam radiotherapy to the neck encompassing a part or whole of the thyroid gland. In this non-randomized prospective study, we have tried to evaluate the response of the thyroid gland to radiation by assessing thyroid function before irradiation and at regular intervals after irradiation. **Aims and Objectives:** The aim of this study were to assess in the cancer patients, who were exposed to the therapeutic external beam radiation, where radiation portals include a part or whole of the thyroid gland: the incidence of primary hypothyroidism, the time required to become hypothyroid, any relation between the total dose for the development of hypothyroidism, and whether there are any patient or treatment-related factors that are predictive for the development of hypothyroidism, including the use of concurrent chemotherapy. **Materials and Methods:** This non-randomized, prospective study was conducted for a period of 2 years in which thyroid function was assessed in 59 patients (cases) of head and neck cancer, breast cancer, lymphoma patients and other malignancies, who had received radiotherapy to the neck region. 59 euthyroid healthy patients (controls) were also taken, who had not received the neck irradiation. These patients/controls were assessed periodically for 2 years. **Results:** The incidence of hypothyroidism after external beam radiation therapy (EBRT) to neck where radiation portals include part or whole of the thyroid gland was 16.94%, seven cases had subclinical hypothyroidism (11.86%) and three cases had clinical hypothyroidism (5.08%). Mean time for development of hypothyroidism was 4.5 months. There was no effect of age, gender, primary tumor site, radiation dose and chemotherapy, whether neoadjuvant or concurrent with the development of hypothyroidism. **Conclusion:** In summary, we found that thyroid dysfunction is a prevalent, yet easily treatable source of morbidity in patients undergoing radiation therapy to neck where radiation portals include a part or whole of the thyroid gland.

Key Words: Chemotherapy, external beam radiation, head and neck cancer, hypothyroidism

Introduction

Hypothyroidism is a known consequence of external-beam radiotherapy to the neck encompassing a part or whole of the thyroid gland. Though hypothyroidism has a significant impact on the quality of life, assessment of thyroid function is not yet a part of continue follow-up of cancer patients even in long term survivors. As the survival of cancer patients are increasing, the quantification of the incidence of radiation-induced hypothyroidism is gaining importance. The most common clinical late-effect of the thyroid gland irradiation in patients exposed to therapeutic doses (30-70 Gy) to the cervical region is primary hypothyroidism. [1] The aetiology of radiation induced thyroid injury includes vascular damage, parenchymal cell damage and auto-immune reactions.

In this non-randomized prospective study, we have tried to evaluate the response of the thyroid gland to radiation by

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assessing thyroid function before irradiation and at regular intervals after irradiation.

Materials and Methods

The present study was conducted for a period of 2 years in which thyroid function was assessed in 59 patients managed in a tertiary care centre. Fifty nine euthyroid healthy control samples were also taken, who had not received the neck radiation. The patients/controls were followed periodically, after the completion of radiation therapy, (in case of patients) first at 3 months, then at 6 months, 12 months, 18 months, and finally at 24-month interval. The following patients were included in the study: Patients with histologically proven non-thyroid malignancies, who were destined to receive EBRT to the primary site as well as to the neck and where radiation portals included a part or whole of the thyroid gland, and patients who euthyroid prior to radiation therapy.

Data analysis

In this study, we present the incidence of long term hypothyroidism in malignancy patients after radiotherapy to the neck. This study also analysed possible factors that affected the development of hypothyroidism. Both serum thyroid stimulating hormone (TSH) and T4 levels were prospectively measured to reveal subclinical and clinical hypothyroidism. Serum thyroid stimulating hormone (TSH) and T4 levels were assayed by Radioimmunoassay method using commercial kits. The radiotherapy technique employed in this study was the conventional EBRT technique using single daily fractions of 1.8-2.0 Gy, with 5 fractions per week using teletherapy cobalt 60 units.

Blood chemistry, complete blood count, abdominal ultrasonography, chest X-ray, ECG, and thyroid hormone levels (TSH, T4 levels), were evaluated regularly. If the patients presented with low T4 levels and clinical symptoms of hypothyroidism, thyroxine was prescribed to relieve the hypothyroidism with subsequent monitoring of serum T4 change at least every 3 months.

Statistical analysis

Various predisposing factors as age, gender, tumor status, primary tumor site, treatment modality, total radiation dose, and chemotherapy were examined for any association with the development of hypothyroidism using Chi-square tests, or Student *t*-test as appropriate. The Kaplan–Meier's method was used to estimate the time from the initiation of treatment to the development of hypothyroidism.

Results

The incidence of hypothyroidism after EBRT to neck where radiation portals include part or whole of the thyroid gland was 16.94%, 7 cases had subclinical hypothyroidism (11.86%) and 3 cases had clinical hypothyroidism (5.08%) [Table 1].

We found no effect of age, gender, primary tumor site, radiation dose and chemotherapy, whether neoadjuvant or concurrent on the development of hypothyroidism. Mean time for development of hypothyroidism was 4.5 months [Table 2].

We observed that 15.25% of patients who developed post therapy hypothyroidism did so within the 1st year. This high rate of early onset of hypothyroidism justifies a policy of early thyroid testing.

Discussion

The first reported case of hypothyroidism following external-beam radiotherapy for malignancy appeared in literature in 1961.[2] Most reports state the incidence to be between 20% and 30%.[3] The incidence of 16.94% found in our study is consistent with these findings.

We evaluated the incidence of hypothyroidism in cases and controls,which was 16.94% in cases and 3.4% in controls. The association of hypothyroidism in the patients who had received radiotherapy to the neck was found to be statistically significant (*P* value 0.015). Both the hypothyroid patients in the control arm were of the subclinical type (3.4%). In the case arm, 7 patients (11.86%) were having

Table 1: Incidence of hypothyroidism after EBRT and mean thyroid hormone levels of cases

Thyroid function	Cases (%)	TSH µIU/ml	T4(T) µg/dl
Euthyroid	49 (83.06)	4.7	8.3
Hypothyroidism	10 (16.94)	24.98	4.38
Subclinical	7 (11.86)	22.77	5.30
Clinical	3 (5.08)	30.16	1.10

TSH: Thyroid stimulating hormone, EBRT: External beam radiation therapy

Table 2: Hypothyroidism covariates evaluated in cases

Risk category	Sub-category	Overall (n)	Hypothyroidism	P value
Overall	Cases	59	10 (16.94)	0.015
	Controls	59	2 (3.4)	
Age (years)	<50	29	5 (17.2)	0.61
	≥50	30	5 (16.70)	
Gender	Male	25	6 (24)	0.18
	Female	34	4 (11.8)	
Tumor site	Breast	30	3 (10)	0.34
	Head and neck	17	4 (23.5)	
	Lymphomas	12	3 (25)	
Radiation dose (GY)	<45	6	2 (33.2)	0.26
	≥45	53	8 (15)	
Mode of treatment	Radiation only	24	4 (16.7)	0.62
	Chemoradiation	35	6 (17.1)	

subclinical hypothyroidism and 3 patients (5.08%) were having clinical hypothyroidism.

Previous studies on the risk of hypothyroidism after neck irradiation have shown that hypothyroidism is more frequent in women than in men.[4] However, in our cohort of patients, neither age nor sex was of statistical significance and was in consistence with the results of Mercado.[5] In our study, patients with age of <50 years were having a hypothyroidism incidence of 17.2% (5/29) and patients with age of ≥50 years having a hypothyroidism incidence of 16.7% (5/30) with a *P* value of 0.61. Similarly, our incidence of hypothyroidism in male patients was 24% (6/25) and incidence of hypothyroidism in the female patients was 11.8% (4/34) with a *P* value of 0.18.

Radiation dose as a risk factor for the development of hypothyroidism remains controversial. In patients receiving radiotherapy for head and neck cancer, doses exceeding 60 Gy were reported to be associated with an increased rate of hypothyroidism.[6] However, in a prospective study, Tell *et al.*,[7] Wu *et al.*,[8] and Posner *et al.*[4] did not find the radiation dose to be a significant factor. Similarly, in our study, the patients who received radiation dose <45 Gy to neck showed incidence of hypothyroidism to the tune of 33.2%, while those receiving radiotherapy doses of ≥45 Gy were having the incidence of hypothyroidism of 15% with a *P* value of 0.26 which is statistically insignificant.

In our study, 35 patients received chemotherapy in addition to radiation as part of their treatment schedule. 17% (6/35) of patients who received chemotherapy became hypothyroid. 16% (4/24) of the patient who did not receive chemotherapy became hypothyroid. The difference was not statistically significant ($P = 0.62$). Posner *et al.*[4] examined the effect of combination chemotherapy on hypothyroidism in patients with head and neck carcinoma and found no association.

In the present study, we evaluated 59 patients; with 30 patients having breast carcinoma, 17 patients of head and neck cancer and 12 patients of lymphoma, who had received radiotherapy to the neck, encompassing a part or whole of the thyroid gland. We detected an incidence of 10%, 23.5% and 25% in breast CA, head and neck carcinoma and lymphoma, respectively. These findings are similar to the incidences of previously cited literature among the patients of head and neck tumors and Hodgkin's disease.[9] Any predilection of hypothyroidism to a particular tumor site was not statistically significant as our *P* value was 0.34.

In our study, TSH levels did not change in the first 3 months but significantly increased in the subsequent 3 months. Glatstein and associates[10] also observed most cases of high TSH within 1 year. Tamura *et al.*[11] reported that the incidence of high TSH increased from 26% after 2 years to 62% after 6-12 years. Thus, two kinds of radiation induced thyroid damage are proposed: subacute damage and late damage. The former develops in almost all patients, whereas the incidence of the latter varies considerably among different reports. Late damage might proceed by a different mechanism from the subacute damage.

Conclusions

We conclude from the study of thyroid function in cancer patients treated with radiotherapy to the neck that hypothyroidism (both subclinical and clinical) occurs with considerable and poorly acknowledged frequency. We believe that monitoring thyroid function should become a routine procedure in any oncology clinic managing these patients.

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