RESEARCH COMMUNICATION

Thyroid Dysfunction Following Therapeutic External Radiation to Head and Neck Cancer

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Abstract

Aim: The aim of the present study was to evaluate changes in thyroid function in patients with head and neck cancer treated with external beam radiotherapy (EBRT). Materials and Methods: This prospective study was conducted on ninety patients with non-thyroid head and neck cancer who were referred to the department of radiotherapy. Thyroid function tests were conducted before, midway during and after EBRT, with follow up at monthly intervals up to 6 months after the completion of therapy. Results: Serum T_3 and T_4 levels were decreased at completion of EBRT and remained so after 6 months follow up. However, serum TSH levels did not significantly vary. Conclusion: EBRT to the neck region for treatment of head and neck cancer induces hypothyroidism and therefore utmost care must be taken to exclude the thyroid from radiation beams without sparing the tumor as far as possible. The clinical protocol in such cases should include monitoring of T_3, T_4 and TSH levels during and after the EBRT.

Keywords: Thyroid dysfunction - head and neck cancer - radiotherapy

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Introduction

Carcinoma of the head and neck region is the 5th most common malignancy worldwide and the most prevalent cancer in male in this part of India. EBRT is an integral part of management of such malignancies, used either alone in early-stage tumors or in combination with surgery and/or chemotherapy in advanced stages. In EBRT for carcinoma of the head & neck region, target volume of irradiation usually includes part or whole of the thyroid gland leading to its damage. Thyroid hypo function is a common side effect after such irradiation and is reported in the literature for over 40 years, with figures reaching up to 50% of irradiated patients in some works (Tell et al., 2004; Garcia-Serra et al., 2005).

Several studies have been undertaken in the past to determine the functional status of thyroid gland in cancer patients before and after completion of EBRT. Majority of them have reported poor functioning of the thyroid after EBRT where thyroid is included in the irradiation field. There are few reports as well which do not give any changes shortly after EBRT and even several years after. On the other hand long term effects of radiation on thyroid gland by various authors reveal that there is development of thyroid carcinoma.

Hypothyroidism has a significant impact on quality of life for patients. Despite this, tests for thyroid functions are not yet included routinely in the pre- or post- radiotherapy assessment protocols of patients with head and neck cancer.

The aim of the present study was to evaluate the changes in thyroid dysfunction in patients with head and neck cancer treated with radiotherapy and to emphasize the necessity of inclusion of routine thyroid function tests in the follow up of these patients.

Materials and Methods

The present study was carried out on 90 patients with biopsy proven malignancies of head and neck who attended the Radiotherapy Department for radiotherapy. Patients having thyroid metastases, a positive history of thyroid diseases, or thyroid surgery were excluded from this study. 25 normal healthy subjects of both sexes were selected as control group. The control subjects included in this study were asymptomatic persons free from any abnormality on routine examination, not smoking, not on antioxidant supplementation, not taking any drug, alcohol or chewing tobacco and were free from any disease.

Patients were classified according to UICC classification (UICC 1974). All the patients were treated by EBRT using cobalt-60 Teletherapy unit with a rectangular field which included the thyroid gland partially or fully. Blood samples were analyzed for serum triiodothyronine (T_3 , reference range 0.60-1.81ng/ml), serum thyroxin (T_4, reference range 1.9-13.3μg/ml) and serum thyroid stimulating hormone (TSH, reference range 0.35-5.50 μIL/ml) by using direct chemo luminescent technology in all patients

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before EBRT (BT), mid way of EBRT (MT) (30 Gy tumor dose), at completion of EBRT (CT) (60-70 Gy tumor dose) and during subsequent monthly follow up to 6 months.

All values are expressed as mean values with standard deviations (SD). Observations were compared with Student's t test and P values < 0.05 were considered to indicate statistical significance.

Results

In the present study the mean serum T_3 & T_4 levels were found to be decreased during EBRT and at 6 months follow up period as compared to BT. Both serum T_3, T_4 levels were decreased significantly ($p<0.001$, $p<0.005$) at 6 months follow up as compared to the control group (Table 1 and 2). A non significant increase in serum TSH was found at the completion of therapy and in follow up period as compared to the control (Table 3).

As per the histopathological grade of the malignancy as shown in Table 1 to 3, the decrease in the levels of serum T3 and serum T4 at 6 month follow up were more pronounced in poorly differentiated malignancies followed by well differentiated and moderately differentiated malignancies as compared to before therapy. Also, the rise in serum TSH is more pronounced in poorly differentiated malignancies followed by well differentiated and least in moderately differentiated malignancies.

Discussion

Before 1970, hypothyroidism was rarely reported following the treatment of head and neck cancer. Clinicians at that time were unaware of this association, and the thyroid gland was considered a radio-resistant organ. From 1970 to date, many papers have been published reporting the incidence of hypothyroidism after irradiation in patients with cancer of the head and neck region

After EBRT to the neck, the documented incidence of hypothyroidism varies widely, from 03 %, (Zohar et al 1984) to 44 %, (Palmer et al., 1981) When sub-divided, incidence of clinical hypothyroidism (elevated serum Thyroid Stimulating Hormone level and depressed serum Thyroxin level) varies from 5 to 10% (Tami et al., 1992; Vrabec, 1981) and that of sub-clinical hypothyroidism (elevated serum Thyroid Stimulating Hormone level and normal serum Thyroxin level) is about 6% in other series (Liening et al., 1990) . Addition of surgery to the neck region vastly increases the incidence of hypothyroidism but addition of chemotherapy probably has little or no effect (Posner et al., 1984).

The mean serum T_3 & T_4 levels were found to decrease but the decrease was non significant during EBRT as compared to BT, however both serum T_3, T_4 levels were decreased significantly ($p<0.001$, $p<0.005$) at the 6 months follow up as compared to the control group. A non significant increase of serum TSH found at the completion of therapy and in follow up period as compared to the control The decrease in the levels of serum T_3 and serum T_4 were more pronounced in poorly differentiated malignancies followed by well differentiated and then moderately differentiated malignancies. Likewise the rise in serum TSH was more in poorly differentiated malignancies followed by well differentiated and least in moderately differentiated malignancies. Hence, it

Table 1. Statistical Analysis of Serum T_3 in Head & Neck Malignancy

Control	BT	MT	CT	1M	2M	3M	4M	5M	6M
1.16*	1.05	1.04	1.06	0.99	0.94	0.90	0.86	0.81	0.78
0.38	0.30	0.29	0.31	0.29	0.28	0.26	0.27	0.26	0.26
t	1.45	1.63	10.3	2.29	3.18	3.92	4.13	4.70	4.93
P	NS	NS	NS	NS	<0.001	<0.001	<0.001	<0.001	<0.001

BT,Before EBRT; MT,Mid way EBRT; CT,Completion of EBRT; 1M-6M,1 to 6 months follow up; NS, Non Significant; *Data are Mean and SD

Table 2. Statistical Analysis of Serum T4 in Head & Neck Malignancy

Control	BT	MT	CT	1M	2M	3M	4M	5M	6M
7.69*	7.16	7.08	6.89	6.69	6.47	6.28	6.05	6.05	6.03
2.43	1.60	1.73	1.77	1.73	1.70	1.71	1.86	2.06	2.13
	1.29	1.40	1.84	2.31	2.85	3.24	3.45	3.11	3.03
	NS	NS	NS	NS	<0.005	<0.001	<0.001	<0.005	<0.005

Table 3. Statistical Analysis of Serum TSH in Head & Neck Malignancy

Control	BT	MT	CT	1M	2M	3M	4M	5M	6M
2.23*	2.01	2.36	3.08	3.1	3.18	3.28	3.36	3.62	3.69
1.52	1.28	1.64	2.11	2.16	2.30	2.40	2.61	2.92	3.04
	0.73	0.34	1.86	1.86	1.94	2.06	2.02	2.22	2.24
	NS	NS	NS	NS	NS	NS	NS	NS	NS

Table 4. Comparison of Serum T_3 Levels in Head and Neck Malignancy According to Histopathological Grading

	BT			6 Month Follow Up		
	Well	Mod	Poorly	Well	Mod	Poorly
Mean	1.04	1.06	1.04	0.74	0.86	0.62
SD	0.33	0.29	0.32	0.24	0.24	0.33
t				2.95	3.05	2.91
P				<0.005	<0.005	<0.005
% (↑ / ↓)				40.5 ↓	23.2 ↓	67.7 ↓

Table 5. Comparison of Serum T_4 Levels in Head and Neck Malignancy According to Histopathological Grading

	BT			6 Month Follow Up		
	Well	Mod	Poorly	Well	Mod	Poorly
Mean	7.16	7.24	6.91	6.08	6.36	5.1
SD	1.7	1.65	1.42	2.32	1.95	2.3
t				1.60	2.12	2.49
P				NS	NS	NS
% (↑ / ↓)				17.7 ↓	13.8 ↓	21.3 ↓

Table 6. Comparison of Serum TSH Levels in Head and Neck Malignancy According to Histopathological Grading

	BT			6 Month Follow Up		
	Well	Mod	Poorly	Well	Mod	Poorly
Mean	2.24	1.62	3.00	3.92	2.69	6.13
SD	1.46	0.94	1.45	2.99	2.24	3.87
t				2.26	2.93	2.93
P				NS	<0.005	<0.005
% (↑ / ↓)				42.9 ↑	39.8 ↑	51.1 ↑

was observed that the alteration in the levels of thyroid profile due to the therapeutic irradiation for head & neck malignancy affects the thyroid gland more in patients who had poorly differentiated malignancies.

Recently Koc and Capoglu (2009) observed thyroid dysfunction in patients treated with EBRT for neck. In their study the median time for development of clinical hypothyroidism was 15 months (range, 0-36 months) and subclinical hypothyroidism was 3 months (range, 0-24 months). Alkan et al., (2008) reported the average time to detection of hypothyroidism was 6 months after the completion of radiotherapy.

Cinar et al., (2003) studied the effect of laryngectomy and postoperative EBRT on thyroid gland functions. In their study, following EBRT serum thyroid stimulating hormone (sTSH), free triiodothyronine (FT_3), and free thyroxin (FT_4) levels were measured every three months at least for a year. Detection of increased levels of serum TSH together with decreased or normal levels of FT_3 and/or FT_4 indicated clinical and subclinical hypothyroidism respectively.

Most of the abnormalities noted by others consisted of elevated serum TSH values but normal T_3 concentrations, the patients being clinically euthyroid. A smaller number of patients had subnormal T_3 and/or subnormal T_3-r values with supranormal TSH levels. Those in the latter group were more likely to have clinical symptoms and signs of hypothyroidism, yet clinical features were frequently vague nonspecific and minimal (Nelson et al., 1978). They further observed that irradiation could produce not only subclinical but also frank hypothyroidism.

Glatstein et al., (1971) recorded spontaneous recovery from abnormal TSH and postulated that excretion of the iodide load may allow a return to normal thyroid function. Turner and Jones (2008) reported 14.3% incidence of clinical and 23.8% sub-clinical hypothyroidism following EBRT to the whole of the thyroid gland. They estimated that by 5 years up to 40% of the patients may become hypothyroid. Further they did histological examination of the thyroid gland after EBRT to document follicular cell damage and vascular damage following doses as low as 225 cGy.

The mechanism of hypothyroidism due to EBRT is also incompletely understood. This may be due to direct follicular destruction or prevention of cell division or vascular damage to the thyroid gland or immunologically mediated damage to the thyroid gland or a various combination of the factors. An immunological influence has been suggested by Einhorn and Wikholm (1967). Because adult thyroid cells in vivo are not expected to have a high turnover rate and are well differentiated, it has been postulated that they may undergo radiation induced apoptosis, varying between different patients.

The common signs & symptoms of hypothyroidism e.g. depression, lethargy, skin changes, constipation, weight gain (>10% of original body weight) etc. are ill defined and can be easily overlooked in cancer patients. Because there is a high rate of co-morbidity in them and the disease and its' treatment may have nutritional, physical and psychological consequences in these patients, that may easily mask the clinical features of hypothyroidism. For these reasons, clinical examination of the cancer patients for features of hypothyroidism is not a reliable one.

In conclusion, many patients with head and neck cancer receive radiotherapy; in most cases, the irradiation field includes the thyroid gland. As a significant number of patients develop hypothyroidism as a side effect following EBRT careful exclusion of the thyroid from radiation fields should be attempted whenever possible and thyroid function tests should be included in the routine follow up protocol of such patients.

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