Thyroid Dysfunction Following Radiotherapy and Combined Therapy in Non-Thyroid Head and Neck Cancers

https://doi.org/10.47210/bjohns.2023.v31i2.921

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ABSTRACT

Introduction

In patients with head and neck cancers thyroid gland bears the brunt in terms of either excision or irradiation resulting in loss of functionality of the gland leading to thyroid dysfunction. The purpose of this study was to evaluate thyroid function following radiotherapy and combined therapy in non-thyroid head and neck cancers.

Materials and Methods

It was a prospective study of 51 patients with head and neck cancers for duration of one year. Thyroid function tests were done before and at the end, 3 months and 6 months following treatment.

Results

Out of 51 patients, 47 (92.15 %) were males and 4 (7.8 %) were females. All the patients received radiation to the neck to a dose of > 50 GY. 36 patients received concurrent chemotherapy and 7 patients underwent surgery. 4 patients were found to have clinical hypothyroidism, 16 patients subclinical hypothyroidism, 1 patient clinical hyperthyroidism and 1 patient subclinical hyperthyroidism. Thus a total of 22 patients developed thyroid dysfunction (P value of 0.001).

Conclusion

Recognizing thyroid dysfunction early and treating it prevents thyroid dysfunction related complications. Hence, thyroid function tests should be done routinely during follow-up in head and neck cancer patients receiving radiotherapy.

Keywords

Head and Neck Cancers; Thyroid Dysfunction; Radiotherapy; Chemotherapy

Thyroid gland is the largest pure endocrine gland in the human body situated in the anterior of neck in front of trachea.[1]

Head and neck cancers rank fifth among all malignancy worldwide and commonest malignancy among Indian males. This is probably due to increased use of tobacco and Gutka in various forms.[1,2] The management of head and neck cancer includes radiotherapy, chemotherapy, surgery and a combination of these. Radiotherapy is one of the most important modalities of treatment of head and neck cancers, besides surgery. Majority of head and neck cancers are locoregionally advanced at the time of diagnosis. Hence radiotherapy treatment field covers the primary site of the tumor and whole neck including the thyroid gland.[3]

The nonsurgical treatment modality for advanced head and neck cancer is concurrent chemo radiotherapy approach. It improves both loco regional and overall survival for patients with locally advanced head and neck cancer. The chemotherapeutic agent used to improve radiation effect and improve overall survival in head and

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neck cancers are the platinum group of drugs especially cis-platin. Radiation therapy is one of the treatment-modality for patients with head and neck cancer. It is used as curative as well as palliative treatment. It was estimated that over 60% of patients with cancer will have radiotherapy as part of their total course of treatment.[4]

The most common clinical late effect of thyroid gland irradiation in patients exposed to therapeutic doses is hypothyroidism.[1] Though adult thyroid cells are relatively radio-resistant due to their low proliferative index, hypo-function of the thyroid gland is a known side effect of radiotherapy to the head and neck malignancies for more than 40 years.[2]

Thyroid dysfunction can occur from direct radiation damage to the thyroid gland and or direct functional damage to the hypothalamic-pituitary axis.[5] The incidence of hypothyroidism is 27%-38% after radiation alone and 40-67% for the combination of radiotherapy and surgery.[6] Incidence of radiation induced subclinical hypothyroidism is 4%-79%.[7] A number of studies done as early as 1960s have reported the development of hypothyroidism after radiotherapy for head and neck malignancies with an incidence of 3 to 47%.[1]

Hyperthyroidism has also been reported following radiotherapy of patients with head and neck squamous cell cancers with a 17.5% incidence of subclinical hyperthyroidism.[8]

This may occur due to radiation induced thyroiditis. Hyperthyroidism may be classified as overt hyperthyroidism which is defined as high serum T3, T4 and low serum TSH concentrations and subclinical hyperthyroidism which is defined as normal T3, T4 and low serum TSH concentrations.[9]

Hence, the purpose of this study was to evaluate thyroid function following radiotherapy to the neck with or without chemotherapy and or surgery and usefulness of thyroid function tests (TSH, FT3, FT4) in identifying and treating patients with subclinical thyroid dysfunction and to stress upon the necessity of including thyroid function tests as part of follow-up.

Materials and Methods

The present study was a prospective study and was conducted on 51 patients with Non-thyroid Head and Neck Cancers from November 2019 to October 2020. The Study was conducted after taking approval from the Institutional Ethics Committee and in accordance with the principles of Helsinki Declaration 1975. 51 patients with Biopsy/ FNAC proven Non-thyroid head and neck cancers in the age group of 23-80 years, both the sexes with pre-treatment normal thyroid function receiving external beam radiotherapy to the neck with or without chemotherapy and or surgery were included in the study. The patients with pre-existing thyroid disease, previous thyroid surgery and history of previous radiotherapy or chemotherapy for Head and Neck malignancy were excluded from the study. Thyroid function tests (TSH, FT3, FT4) were done before treatment in all the cases. The patients were divided into three groups on the basis of the type of treatment. Those receiving Radiotherapy only (n=8), those receiving concomitant Chemotherapy and Radiotherapy (n=36) and those receiving Radiotherapy after Surgery (n=7).

The patients were treated with Cobalt 60 teletherapy machine with conventional fractionation of 1.8-2 GY/Fr/ day for 5 days a week for 6-7 weeks. The treatment portals included the primary tumor with margin and the whole neck. The treatment intent was either radical or postoperative adjuvant with or without chemotherapy using weekly Cisplatin at 40 mg/m^2 of body surface area for six cycles. Thyroid function tests consisting of a baseline serum thyroid stimulating hormone (TSH, Reference range 0.35-5.5mIU/ml), free tri-iodothyronine (FT3, Reference range 2.3-4.2 pg/ml), free thyroxine (FT4, Reference range 0.89-1.76ng/dl) were performed in all patients before and after treatment. Patients were evaluated and followed with blood samples for thyroid function estimation at the end of the treatment and thereafter at 3 months and 6 months following the treatment. Thyroid function tests were done in Biochemistry Laboratory using radioimmunoassay kits and automated analyzer was used to calculate the values. Data was entered in Microsoft Excel spread sheet and analyzed and compared using the statistical package for social sciences (SPSS) software (version 21 for windows).

Results

In our study, 51 patients with non-thyroid head and neck cancers were selected as per the inclusion criteria. Of the 51 patients, 47 (92.15%) were males and 4 (7.8%) were females. The patients were in the age group of 23 to 80 years with mean age among males 57.19 ± 11.94 years and among females mean age was 56.75 ± 12.57 years. The majority of the patients were in the age group of 41 to 60 years.

In the present study the occurrence of thyroid dysfunction was the highest in the age group of 41-60 years (12) followed by 61-80 years (9). This analysis showed that thyroid dysfunction is common in elderly and old age groups as compared to young. Hence age is a significant factor in the development of thyroid dysfunction.

The results of our study suggest that hypothyroidism is strongly associated with non-thyroid head and neck cancer treatment. (Table I).

Table I : Thyroid dysfunction before and after treatment

TREATMENT STATUS	HYPO-THYROIDISM	HYPER-THYROIDISM	NORMAL	TOTAL
Before treatment	0	0	51	51
After treatment	20	2	29	51
p-value	P = 0.001			

Table II : Occurrence of thyroid dysfunction on the basis of treatment modality and radiation dosage

TREATMENT MODALITY	CLINICAL HYPO-THYROIDISM	SUBCLINICAL HYPO-THYROIDISM	CLINICAL HYPER-THYROIDISM	SUBCLINICAL HYPER-THYROIDISM	NORMAL	TOTAL
RT (n=8)	0	5	0	0	3	8
CCRT (n=36)	4	7	1	1	23	36
Surgery with Adjuvant RT (n=7)	0	4	0	0	3	7
Total	4	16	1	1	29	51
P-Value	0.0008					

RT = Radiotherapy, CCRT = Concurrent chemo-radiotherapy

The incidence of thyroid dysfunction in general population is 0.02% with female preponderance. In our study 21 (44.68%) out of 47 male patients and 1 (25%) out of 4 female patients developed thyroid dysfunction with subclinical hypothyroidism being the most common. The radiation dose in RT group and CCRT group was 70

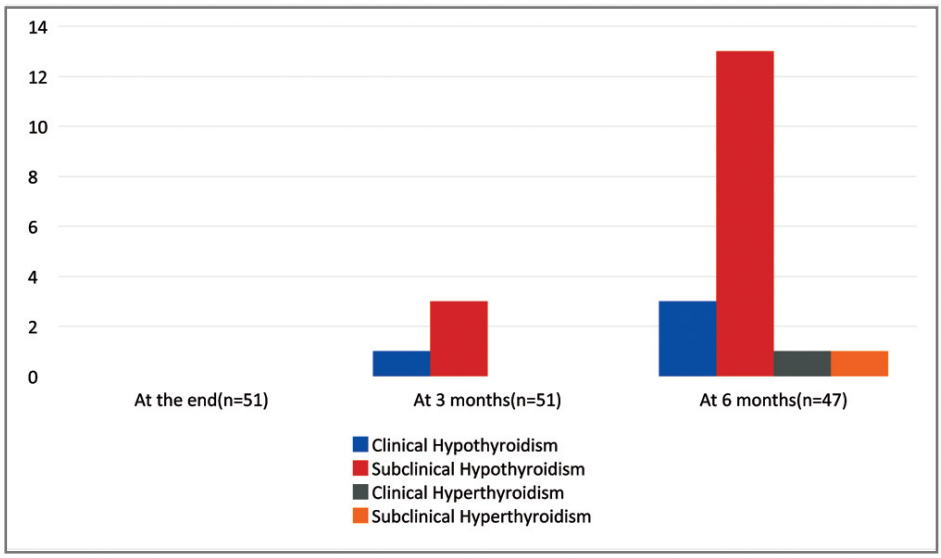

Fig. 1. Time of onset of thyroid dysfunction after completion of treatment.

GY in 35 fractions for 7 weeks, whereas in surgery with postoperative RT group, dose was 54 GY in 27 fractions for 5.2 weeks (Table II).

In our study thyroid dysfunction developed as early as 3 months after the completion of treatment with majority of the patients developing thyroid dysfunction at 6 months after the completion of treatment (Fig. 1).

The mean ± standard deviation (SD) of TSH, FT3 and FT4 among RT, CCRT and surgery with postoperative radiotherapy groups were analyzed and compared before and at the end, at 3 months and at 6 months after the completion of treatment. The result was statistically highly significant on the basis of mean TSH values among the three groups (P=0.0001) (Table III).

Table III : Mean (±SD) of thyroid function tests (TSH, FT3, FT4) for operated and non-operated patients

TSH	BEFORE TREATMENT		AT THE END OF TREATMENT		3 MONTHS AFTER COMPLETION OF TREATMENT		6 MONTHS AFTER COMPLETION OF TREATMENT		P VALUE
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
RT	2.63	0.88	2.42	1.00	2.81	0.85	7.4	4.59	0.0001
CCRT	2.12	1.23	2.1	1.16	2.56	1.96	9.27	19.30	0.0001
Surgery + Adjuvant RT	1.57	0.96	2.33	0.89	13.17	19.38	10.53	11.01	0.0001

Table III (Contd.)

Table III (Contd.) : Mean (±SD) of thyroid function tests (TSH, FT3, FT4) for operated and non-operated patients

TSH	BEFORE TREATMENT		AT THE END OF TREATMENT		3 MONTHS AFTER COMPLETION OF TREATMENT		6 MONTHS AFTER COMPLETION OF TREATMENT		P VALUE
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
FT3									
RT	2.65	0.24	2.63	0.19	2.65	0.29	2.74	0.45	0.89
CCRT	2.62	0.26	2.60	0.24	2.63	0.26	2.63	0.29	0.93
Surgery+ Adjuvant RT	2.55	0.16	2.49	0.15	2.68	0.22	2.60	0.26	0.76
FT4									
RT	1.10	0.19	1.09	0.12	1.08	0.12	1.07	0.13	0.97
CCRT	1.11	0.17	1.11	0.14	1.10	0.16	1.06	0.29	0.89
Surgery+ Adjuvant RT	1.04	0.07	1.05	0.11	1.13	0.08	1.15	0.13	0.02

Table IV : Mean (± SD) of thyroid function tests (TSH, FT3, FT4) for operated patients with and without thyroid surgery

TSH	BEFORE TREATMENT		AT THE END OF TREATMENT		3 MONTHS AFTER COMPLETION OF TREATMENT		6 MONTHS AFTER COMPLETION OF TREATMENT		P VALUE
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
Total laryngectomy with hemit-hyroidectomy with adjuvant RT	1.51	1.15	3.09	0.37	28.45	22.68	18.11	12.40	0.001

Table IV (Contd.)

Table IV (Contd.) : Mean (± SD) of thyroid function tests (TSH, FT3, FT4) for operated patients with and without thyroid surgery

TSH	BEFORE TREATMENT		AT THE END OF TREATMENT		3 MONTHS AFTER COMPLETION OF TREATMENT		6 MONTHS AFTER COMPLETION OF TREATMENT		P VALUE
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
Surgery other than laryngectomy with adjuvant RT	1.62	0.97	1.77	0.72	1.72	0.63	4.8	6.29	0.45
FT3									
Total laryngectomy with hemit-hyroidectomy with adjuvant RT	2.59	0.12	2.51	0.18	2.75	0.34	2.71	0.37	0.07
Surgery other than laryngectomy with adjuvant RT	2.50	0.19	2.48	0.15	2.64	0.11	2.50	0.15	0.76
FT4									
Total laryngectomy with hemit-hyroidectomy with adjuvant RT	1.01	0.02	1.03	0.06	1.08	0.05	1.07	0.10	0.53
Surgery other than laryngectomy with adjuvant RT	1.07	0.09	1.08	0.15	1.16	0.09	1.14	0.16	0.99

Since all the patients received radiotherapy either alone or in combination, so we can conclude that radiotherapy is strongly associated with the development of thyroid dysfunction.

The mean± standard deviation (SD) of thyroid function tests in patients who underwent total laryngectomy with hemithyroidectomy with postoperative radiotherapy and in those who underwent surgical procedures other than laryngectomy were analysed and compared. (Table IV).

This suggests that the surgical procedures involving thyroid surgery are significantly related to the development of thyroid dysfunction.

Discussion

The effects of ionizing radiation on thyroid gland in therapeutic neck irradiation (40-70 GY) leads to hypothyroidism. The impact of post irradiation hypothyroidism was first reported in 1929.[1] The first case of hypothyroidism in patients treated for head and neck malignancy was reported in literature in 1961.[10]

Documented incidences of primary hypothyroidism after radiotherapy have varied from 3% to 47%. Most of the investigators have reported an incidence of 20% to 30%.[11]

Our study shows 39.21% incidence of hypothyroidism comparable with literature above. In general, the external irradiation of the normal thyroid may cause dysfunction of the gland within months to years following treatment.

In our study, the incidence of hypothyroidism was 39.21% which is comparable to that of Glatstein et al.[12] who reported 44% incidence of hypothyroidism after irradiation of the neck for Hodgkin's disease.

The study with the longest follow-up of patients was presented by Einhorn J and Wikholm G[13] who studied 41 patients of carcinoma larynx and hypopharynx treated with radiotherapy (RT) with 10-year follow-up, the incidence of established hypothyroidism was 7.3%.

Alterio et al[14] stated that among thyroid disorders, primary hypothyroidism seems to be the most frequent late effect with an incidence of 20% to 30%.

Our study found that elderly age group is affected more compared to young and old age groups, this is supported by the study done by Mercado et al.[15] Our results are also in-agreement with that of Colevas et al.[16] who reported an increased incidence of hypothyroidism in 60 years age group.

In our study, the incidence of hypothyroidism was 40.4% in males and 25% in females suggesting that female gender has no significant impact on the development of post-irradiation hypothyroidism. This is in concordance with other studies like Tell et al.[17] and Bhatia et al.[18] who did not found any significant relationship between gender and development of hypothyroidism post irradiation.

In our study, the incidence of hypothyroidism was 62.5% following radiotherapy alone which is in total agreement with that of Schimpff et al.[19] who reported 64% incidence of hypothyroidism following radiotherapy alone in patients with Hodgkin's disease.

In our study, the incidence of hypothyroidism was 30.55% in patients who received concurrent chemoradiation (CCRT) which is similar to that of Srikantia et al.[20] who reported an incidence of 31.25% of hypothyroidism and Turner et al.[21] who found 36% incidence following chemoradiation. 2 (5.55%) patients in CCRT group developed hyperthyroidism which is comparable to Alterio et al.[14] who found 10.8% incidence of hyperthyroidism following external beam radiotherapy. However, the sample size was small and the follow-up period was comparatively short in our study, this needs a separate study with a large sample size and a longer follow-up in future.

In our study, the incidence of hypothyroidism was 62.5% in patients who received radiotherapy alone as compared to only 30.55% in patients who received concurrent chemo-radiotherapy suggesting that the combination chemotherapy had no significant effect on the thyroid gland in patients with head and neck malignancy, which is in-agreement with that of Posner et al.[6]

Weissler MC and Berry BW,[22] Sinard et al.[10] and Tell et al.[17] who found similar results. Aich et al.[2] on the contrary had a 21% incidence with addition of chemotherapy as compared with 16% with radiotherapy (RT) alone.

In our study, the incidence of hypothyroidism was 57.14% in patients who underwent surgery with adjuvant radiotherapy and the incidence was 100% in patients who underwent total laryngectomy with hemithyroidectomy with adjuvant radiotherapy which is supported by other studies like Posner et al.[6] who reported 100% incidence and Weissler MC and Berry BW[22] who had 92% incidence of hypothyroidism after total laryngectomy with hemithyroidectomy with adjuvant radiotherapy, whereas none of the patients who underwent neck dissection developed thyroid dysfunction which is in agreement with Weissler MC and Berry BW[22] who found similar results. Lin et al.[23] on contrary found significantly higher risk of thyroid dysfunction after primary tumor excision with neck dissection (PTE+ND).

We analyzed the occurrence of hypothyroidism, both clinical and subclinical against the radiation dose, it was found to be non-significant. This is supported by Mercado et al.[15] In their study of 155 patients, they observed that the likelihood of developing hypothyroidism could not be predicted according to radiation dosage to the primary site or to the neck. In a study by Koc M and Capoglu I[8] univariate analysis of various factors failed to identify radiation dose as a relevant risk factor for hypothyroidism.

In our study, the minimum follow-up period was 6 months post irradiation which is lower than other studies. Turner et al.[21] had a mean follow-up of 21 months. In our study 7.84% developed hypothyroidism at 3 months and 34.04% had hypothyroidism at 6 months of follow-up which is comparable to the study done by Rao D and Shah S[1] who had a minimum follow-up period of 9 months and reported 43% incidence of hypothyroidism.

Our results are comparable with that of Colevas et al.[16] who noted 50% incidence of hypothyroidism in the first year and Aich et al.[2] who noted hypothyroidism at 6 weeks post radiotherapy (RT) and at 6 months with concomitant chemoradiation (CCRT).

All of the studies stated that recognizing subclinical hypothyroidism at an early stage and treating the same with thyroxine prevents clinical hypothyroidism and also preventing cardiac events by reducing lipid level, as mentioned by Cooper DS.[24]

Conclusion

Hypothyroidism (clinical or subclinical) is an under rated, neglected under-recognized morbidity of radiotherapy to neck. The incidence is 39.21%. It can occur as early as 3 months following radiotherapy and increases with time. Addition of thyroid surgery has shown to increase the incidence of hypothyroidism, but addition of concurrent chemotherapy had no significant impact on thyroid function. Hereby, we strongly recommend that thyroid function tests should be done routinely in head and neck cancer patients during follow-ups from as early as 3 months and carried lifelong for long-term survivors.

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