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A prospective analysis of thyroid dysfunction after radical radiotherapy in locally advanced head and neck cancer

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Abstract
Aim: Treatment of head-and-neck cancer patients with surgery, radiotherapy (RT), and chemotherapy has been associated with post radiotherapy hypothyroidism (HT). This study was aimed to assess the effect of radiotherapy on thyroid function with head and neck cancer
Material and method: We reviewed the prospectively collected thyroid function data of patients treated with concurrent chemo radiotherapy therapy in head and neck cancers. The incidence of post treatment hypothyroidism was estimated. The patient factor, tumor site, and treatment factors possibly associated with HT were evaluated.
Results: Of 295 patients, 250 were evaluated for radiotherapy induced hypothyroidism. In this study, 37(14.7%) patients out of 250 developed hypothyroidism at median 6 months of follow up. Univariate and multivariate analyses of age and tumor site identified as a clinically relevant risk.
Conclusion: In our study we have recognized hypothyroidism after 3 to 6 months following radiotherapy. Recognizing hypothyroidism (overt or subclinical) early and treating it has benefits. Hence, Thyroid function tests should be made routine and must be started from as early as 3 months.

Keywords: hypothyroidism; radiation therapy; head and neck cancer

Introduction

Curative treatment of patients with advanced locoregional squamous cell carcinoma of the head and neck (SCCHN) is often associated with significant long-term morbidity. Ionizing radiation applied to the head and neck region can cause hypothyroidism, as the thyroid gland is included in the irradiated area [1]. Subclinical hypothyroidism usually develops with elevated thyroid-stimulating hormone (TSH) levels and normal free thyroxin (T4) levels). Subclinical hypothyroidism can remain stable for years or progress to a clinical form with elevated TSH levels with decreased T4 levels [2]. Thyroid dysfunction usually remains undiagnosed for a long time because of symptoms mimic other diagnosis, which include asthenia, depression, fatigue, weight gain, skin changes or dyslipidaemia [3, 4], which are often non-specific, and are attributed to the disease or treatment. Early recognition of hypothyroidism (overt or subclinical) has benefits. Diagnosis during the subclinical phase is very important to avoid evolution to the clinical form [5].

Methods and materials

The study includes a prospective analysis of 250 consecutive head-and-neck cancer patients treated with chemoradiotherapy or radiotherapy at in a tertiary care center of north- west India between May 2019 and April 2020. After approval of institutional Review Board/ Ethical committee, histopathological proven locally advanced head and neck cancer patients who required radiotherapy or chemoradiotherapy and ready to give informed written consent were included in this study. Sample size was calculated 250 subjects as 95% confidence limit and 5% absolute alpha error assuming proportion of hypothyroidism patient with post radiotherapy head and neck cancer 16%. Patients with previous history of neck irradiation or with history any co-morbidity were excluded from study population.

Evaluation

Before initiation of the treatment, all patients underwent complete physical examination and biochemical investigations. A baseline thyroid function tests was done on day 1 at the start of radiotherapy. Further evaluation was done at completion of radiotherapy and 3 & 6 months of follow up. Complete history, physical examination, symptomatic assessment, LFT, RFT, TSH, free T4 and triiodothyronine levels were measured at baseline, 3 and 6 months after completing RT. Based on thyroid hormone values at the last follow-up, patients were then grouped in three categories: (*1*) normal thyroid function (normal levels of TSH and normal levels of thyroid hormones); (*2*) Subclinical hypothyroidism (high level of TSH and normal level of T3 &T4); (*3*) Overt/Clinical hypothyroidism (high level of TSH and low level of FT3 and/or FT4). Patients diagnosed with hypothyroidism were referred to the endocrinology department for further studies.

Eighty nine percent patients received concurrent chemoradiotherapy with cisplatin while 11% patients received only radiotherapy. Cisplatin was given in a dose of 30 mg/m2 on weekly basis during radiotherapy. Radiotherapy was delivered with two lateral parallel opposed fields with Co-60 teletherapy machine. Target volume includes whole neck with spinal cord sparing after 44Gy. Target dose delivered varied from minimum of 44Gy in 22 fractions to maximum of 70 Gy in 35 fractions over a period of 6-7 weeks.

Results

In this prospective, nonrandomized clinical study of 250 patients' median age at presentation was 56.36 years with a range of 29-70 years. Majority of population i.e. 30% was in more than 5th decade age group of life. 20.8% of the populations were having age less than 40 years. In the population studied male: female sex ratio was 4.95. Moderately differentiated squamous cell carcinoma was most common histological subtype with a frequency of 54.4%. Oropharynx (37.2%) was the most common site of tumour followed by larynx (25%) oral cavity (24%) and hypopharynx (14%). Patients' characteristics are shown in Table-1 Among 250 patients, 29(11.6%, p_0.031) patients developed subclinical hypothyroidism with a follow up of 3 months. Later 30 patients (12%, p_0.0231) developed overt hypothyroidism within next 3 month of follow up. Another 7(2.8%) patients develops subclinical hypothyroidism in this duration which was euthyroid in 3 month of follow up (Table-2). Patients with age more than 60 years were more commonly associated with radiotherapy induced hypothyroidism [(p_0.0341) (Figure-1)]. Similarly, incidence of hypothyroidism in male patients was 83.2% (25/30) and incidence of hypothyroidism in the female patients was 16.8% (5/30) with a *P* value of 0.18. Larynx followed by hypopharynx was most common tumour site associated with hypothyroidism (Figure-2). Association of hypothyroidism with site of primary tumour (p_0.0224) and age of patients (p_0.0341) found statically significant.

Table 1: Patients' characteristics

Age	
Range	29-70
Mean age ±SD	54.2 ±.32
Sex	
Male	208 (83.2%)
Female	42 (16.8%)
ECOG score 0.251 (NS)	
0	124(49.6%)
1	98(39.2%)
2	28(11.2%)
Associated habits	
Tobacco	227(90.8%)
Alcohol	176(70.4%)
AJCC stage	
Stage II	10(4%)
Stage III	116(46.4%)
Stage IVA	119(47.6%)
Stage IVB	5(2%)
Primary tumour site	
Oral cavity	60(24%)
Oropharynx	93(37.2%)
Hypopharynx	62(24.8%)
Larynx	35(14%)
Histopathology	
WD SqCC	74(29.6%)
MD SqCC	136(54.4%)
PD SqCC	40(16%)
Thyroid hormone	
TSH	2.53± 0.95
FT3	1.12 ± 0.21
FT4	7.85± 1.39

Discussion

Radiotherapy plays an important role in the management of head and neck cancers. The majority of new cases of head and neck cancer need radiotherapy as a primary treatment, as an adjunct to surgery alone or in combination with chemotherapy. Thyroid gland is a sole critical organ which comes in treatment field and gets damaged either by radiation or surgery during management of tumour. Hypothyroidism after radiation therapy for head-and neck cancer still represent a clinically underestimated problem. Subclinical or overt hypothyroidism, thyroiditis, autoimmune thyroiditis, and thyroid tumors have been reported as sequelae of irradiation to head and neck [6].

The present study is prospective nonrandomized study of histo pathologically proven head and neck cancer patients who received whole neck irradiation. The occurrence of overt and subclinical hypothyroidism in these patients is studied over a follow up period of 6 months following radiotherapy. In our study, at 6 month of follow up, total 14.7% developed subclinical hypothyroidism.

Table 2: Occurrence of hypothyroidism

Outcome	3 month post RT No. (%)	6 month post RT No. (%)
Normal	221 (988.4%)	213 (85.2%)
Subclinical hypothyroidism	29 (11.6%)	7 (2.8%)
Clinical hypothyroidism	0	30 (12%)

Radiation-induced hypothyroidism develops after a median interval of 1.4-1.8 years (range 0.3-7.2 years) [7]. Therefore, it should be stressed that the presented NTCP model can only be used to estimate the risk on hypothyroidism in the first 2 years after completion of radiation therapy.

Colevas et al [8]. Noted that 50% of the patients who developed hypothyroidism did so in the first year. This is one of the few studies which had a high incidence at first year. *Tell et al* [9]. Found that the Kaplan–Meier predictive risk for hypothyroidism after 5- and 10-year post-irradiation was only 20 and 27%, respectively. *Aich et al* [10]. Had an incidence of 16.6% at the end of 2-year follow-up. Reports have shown that the incidence of hypothyroidism is approximately 14% in patients receiving radiotherapy alone and up to 100% in patients treated with surgery and radiotherapy [11, 12]. *Smolarz et al* [12]. Reported a higher incidence (34%) of hypothyroidism in patients treated with surgery and radiotherapy and a lower incidence (7%-13%) in patients treated with radiotherapy or surgery alone.

In our study patients with age more than 60 years were significantly associated with radiotherapy induced hypothyroidism [(p_0.0341) (Figure-1)]. The incidence of hypothyroidism in male patients was 83.2% (30/37) and incidence of hypothyroidism in the female patients was 16.8% (7/37) with a *P* value of 0.678.

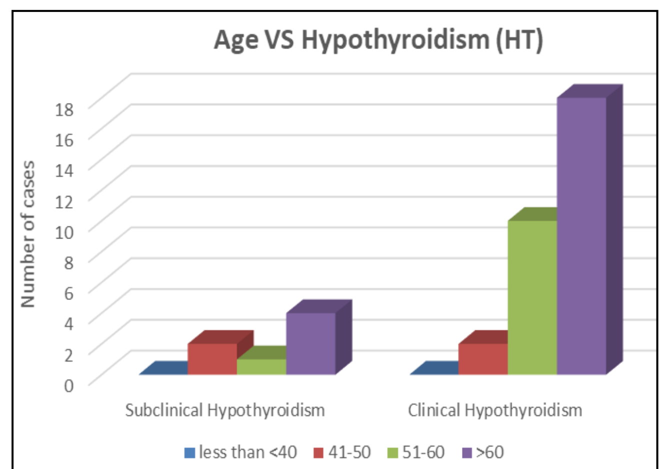

Fig 1: Age VS Hypothyroidism

Colevas et al [8]. Results suggest an influence of age on the

rate of HT in both univariate and multivariate analyses; the association was weak, unless age was treated as a discontinuous variable.
However, *in B A Laway et al*.[13]cohort of patients, neither age nor sex was of statistical significance and was in consistence with the results of *Mercado* [14]. In the study by *Chao yeuh*, female sex was a risk factor for developing hypothyroidism [15].
In our study, 90% cases of hypothyroidism were associated with larynx and hypopharynx. Oral cavity (2%) was the least common association in tumour sites. The association of hypothyroidism was statically significant [(0.0224) (Figure-2)].

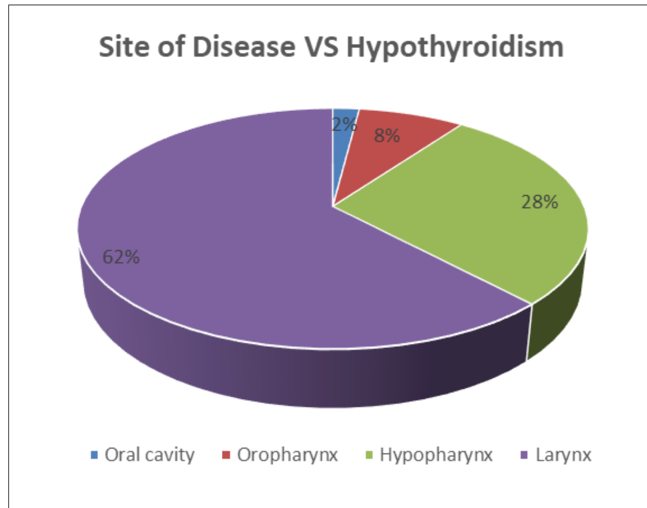

Fig 2: Site of disease VS Hypothyroidism

J R Alba [16] found that among the tumour-related variables, only tumour location was significantly associated with the development of hypothyroidism. Of those who developed hypothyroidism, 72% had laryngopharyngeal tumours, 23.2 % laryngeal site, 10% nasopharyngeal tumours, 4.9 % pharyngeal, 1.3% had adenopathy of unknown cause, 1.2% oral cavity tumours and 0.5% had a parotid tumour. *Shrikantia et al* [17]. found hypopharynx followed by larynx as most common site for radiation induced HT and found that primary site of the tumor was not a significant factor as all the patients received whole-neck irradiation and hence uniformity in the volume of thyroid irradiated. *Murthy 18*[] *et al* and *Kanti et al* [19]. Had a higher percentage of cancers arising larynx and laryngopharynx.
In this study the baseline mean values for T3, T4 and TSH were 1.2, 7.85 and 2.53 respectively. After 3 moth post radiotherapy TSH was slightly raised with mean value 3.73. Clinical hypothyroidism was established by 6 moth post radiotherapy with stable T3, decreased T4 (mean value 2.92) and increased TSH [(mean value 6.74) (Table-3)].

Table 3: Thyroid Hormone

Thyroid hormone	Baseline		3 Month post RT		6 Month post RT	
	Mean	SD	Mean	SD	Mean	SD
T3	1.12	0.21	1.12	0.21	1.08	0.17
T4	7.85	1.39	6.83	1.38	2.92	1.85
TSH	2.53	0.95	3.73	1.51	6.74	2.14

Leining et al [20]. Reported subclinical hypothyroidism after radiotherapy in 26% of patients; the majority of the patients had subclinical hypothyroidism manifested by an elevated TSH. *Weissler et al* [21]. Reported that 57% of the patients developed elevated TSH levels within 6 months to 1 year of treatment. In literature documented incidence of hypothyroidism varies between 3% and 79%. *Colevas et al* [8]. Noted that 50% of the patients with raised TSH and FT4 levels in first year post radiation. *Glatstein and associates* [22] also observed similar finding. *Alkan et al* [23]. Reported an average time to detection of hypothyroidism of 6.08 ± 5.4 months (range 4-24) after completion of radiotherapy.
However, in our cohort of patients, tumour stage, grade and sex were not of statistical significance and were in consistence with the results of *Laway et al* [13]. and *Mercado et al* [14].

Conclusion

Radiation induced hypothyroidism is seen as a late complication of radiation. Within 6 months of follow up, most of literature says the occurrence of radiation induced subclinical hypothyroidism. Recognizing hypothyroidism (overt or subclinical) early and treating it has benefits. Hence, Thyroid function tests should be made routine and must be started from as early as 3 to 6 months. Hence, Thyroid function tests should be made routine and must be started from as early as 3 months.

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