



PROSPECTIVE STUDY OF THYROID DYSFUNCTION IN POST RADIOTHERAPY PATIENTS WITH HEAD AND NECK CANCERS

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ABSTRACT

Introduction: Head and neck squamous cell carcinoma ranks 6th among all malignancies worldwide , highest noted among Indian males. At the time of diagnosis, majority of head and neck tumors are locoregionally advanced where radiotherapy with or without chemotherapy is the major treatment modality.

Hypothyroidism is one of the late side effects in patients exposed to therapeutic doses of RT to the neck. The effect may be clinical or sub clinical hypothyroidism. Sub clinical hypothyroidism evolves to clinical hypothyroidism at the rate of about 5 to 20% per year.

Thus, as Radiation Induced Hypothyroidism will markedly influence the quality of life , hence emphasizing the need for thyroid function test during the follow up .

Aim of the study : To determine the magnitude of hypothyroidism following RT to the neck, To assess the mean time period for the development of hypothyroidism following RT to the neck. The need for routine performing of TFT during follow-up period .

Materials and methods : This is a prospective study of 50 patients of histopathologically proven head and neck cancer , receiving radiotherapy in our hospital from December 2016-July 2017. Thyroid function test were done at baseline and at 3 wks, 3 months and 6 months following radiotherapy.

Results: Eight (16%) out of 50 patients were found to have hypothyroidism which was strongly significant with the p value of 0.022.

Conclusion : Hypothyroidism can occur as early as 6 months following RT.

Patients receiving both lateral and central neck radiation are more prone for Hypothyroidism.

Thyroid function tests should be made routine prior RT and during follow up period as early as 6 months and carried out lifelong.

KEYWORDS : Head and Neck Cancer , Thyroid dysfunction ,post radiotherapy.

Introduction :

Head and neck squamous cell carcinoma ranks 6th among all malignancies worldwide , highest noted among Indian males .Tobacco smoking and alcohol are the main risk factors and their effects are synergistic.

The different modalities of treatment for head and neck cancer include surgery, radiotherapy(RT) , chemotherapy and combination of these. At the time of diagnosis, majority of head and neck tumors are locoregionally advanced where radiotherapy with or without chemotherapy is the major treatment modality. Incidental exposure of nontarget tissues and organ will happen even in the most modern radiation therapy . Such an inadvertent consequence of external beam radiotherapy is irradiation to the thyroid gland.

The first case of radiation induced hypothyroidism was reported in 1929 by Felix et al ,after therapy for laryngeal carcinoma. Hypothyroidism is one of a late complication of exposure to therapeutic doses of RT to the neck. The risk factors for developing hypothyroidism are total radiotherapy dose ,irradiated volume of thyroid gland ,location of radiation field , the extent of prior thyroid resection and addition of chemotherapy. The mechanism of post RT thyroid dysfunction is radiation – induced vessel damage ,fibrosis of gland's capsule or autoimmune reaction.

The effect may be clinical hypothyroidism , with high thyroid – stimulating hormone (TSH) and low thyroxine (T4) and the presence of clinical symptoms or sub clinical hypothyroidism , with high TSH and normal T4 level with no noticeable symptoms by the patient .Symptoms include fatigue , cold intolerance , weight gain , skin dryness , slowed mentation, depression, pleural and pericardial effusions, decreased gastrointestinal motility, congestive heart failure and acceleration of atherosclerosis .Sub clinical hypothyroidism evolves to clinical hypothyroidism at the rate of about 5 to 20% per year.

Thus, as Radiation induced hypothyroidism will markedly influence the quality of life, hence emphasizing the need for thyroid function test

during the follow up .

MATERIALS AND METHODS:

A prospective study conducted in Vijayanagara Institute of Medical Sciences, Ballari, Karnataka with 50 patients of histopathologically proven head and neck cancer receiving external beam to whole neck on telecobalt between December 2016 to July 2017.

Inclusion criteria : patients of any age , both sexes receiving external beam radiotherapy to the neck .all patients had normal thyroid function test before RT.

Exclusion criteria: prior radiotherapy to head and neck ,recurrent disease, previous history of thyroid surgery , pre existing thyroid disease.

Thyroid function test was prospectively evaluated by measuring TSH(normal range,0.4 – 4.20micro IU/ml),T4(normal range,4.8-11.6n g / ml),T3(normal range,0.5-1.85ng/ml)before start of RT and periodically after completion of RT at 3 weeks , 3 months and 6 months. Total T4 and T3 estimation was done using the Radioimmunoassay kits and TSH estimation was done using immunoradiometric assay .

Patients were treated with Cobalt 60 teletherapy unit with conventional fractionation of 1.8 to 2 Gy/Fr/day for 5 days a week. The treatment portals included the primary tumor with margin and the whole neck. For primary and the upper neck with two lateral portals and lower neck with separate central portal. The treatment intent was only radical radiotherapy with or without concurrent chemotherapy with weekly cisplatin at 40 mg/m³ of body surface area.

STATISTICAL METHODS :

Results will be presented in number, percentage and mean. Chi square test is applied for final statistical association using openepi 6.0 version.

Results :

In this prospective clinical study of 50 patients, 46(92%) were males

and 4(8%) were females and majority were in the age group of 41 to 60years.Carcinoma hypopharynx (26%) was primary in majority of the patients [Table-2].

The patients were followed up for a period of six months to determine the occurrence of sub clinical hypothyroidism. Eight (16%) patients were found to have hypothyroidism which was strongly significant with the p value of 0.022[Table-3,chart no 1] .Six (12%) were found to have sub clinical hypothyroidism.

Among the patients who developed hypothyroidism, 4 of 8 were in the age group of 41 to 60 years [Table-4,chart no 2]. Only males developed hypothyroidism [Table-5].Both age and sex factor were not significant. Among the patients who developed hypothyroidism, 4(8%) were of glottic Ca and 4(8%) were of hypopharyngeal Carcinoma. Hence primary site of tumor was not significant. Patients who received central and lateral neck radiation developed hypothyroidism. This was strongly significant with a P value of 0.00065[Table-6, chart no 3]. All the patients who developed hypothyroidism were considered for hormone-replacement therapy, based on the American Association of Clinical Endocrinologists and The American Thyroid Association (ATA/AACE) Guideline for hypothyroidism [1].

TABLE : 1

Patient characteristics	N(%)
Sex	
Male	46(92%)
Female	4(8%)
Total	50
Age	
21 to 40	6(12%)
41 to 60	27(54%)
> 60	17(34%)
Total	50

Patient characteristics

TABLE 2

Primary site	N(%)	Patients with hypothyroidism Number (%)	P value
Oral cavity Ca	9(18%)	0(0)	0.3664
Oropharynx Ca	6(12%)	0(0)	0.3664
Supra glottic Ca	11(22%)	0(0)	0.3664
Glottic Ca	11(22%)	4(8%)	0.848
Hypopharyngeal Ca	13(26%)	4(8%)	0.848
Ca - carcinoma			

Occurrence of hypothyroidism according to primary site of tumor

TABLE 3:

Outcome	Before RT	6 wks post RT	3 months post RT	6 months post RT
Normal	50	50	50	42
Hypothyroidism	0	0	0	8

Occurrence of hypothyroidism

TABLE 4:

Age in years	No of patients	Patients with hypothyroidism Number (%)	P value
21- 40	6	1(2%)	0.96
41- 60	27	4(8%)	0.8414
>60	17	3(6%)	0.839

Occurrence of hypothyroidism according to age

TABLE : 5

Gender	No of patients	Patients with hypothyroidism Number (%)
Male	46	8(16%)
Female	4	0(0)

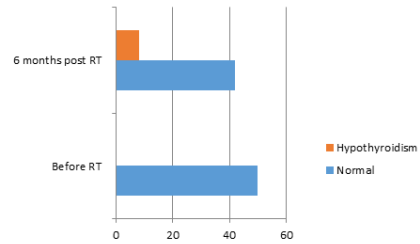
Occurrence of hypothyroidism according to gender

TABLE : 6

Pattern of radiotherapy	No of patients	Patients with hypothyroidism Number (%)	P value
Central + lateral	21	8(16%)	0.00065
Only lateral	29	0(0)	

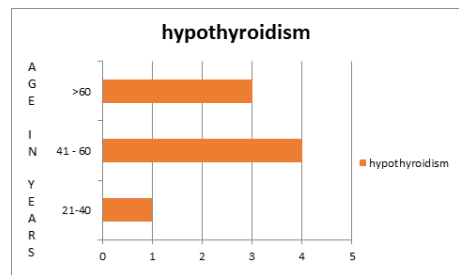
Occurrence of hypothyroidism according to pattern of radiotherapy

Chart no : 1



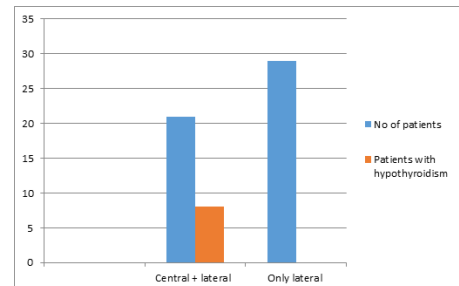
Occurrence of hypothyroidism

Chart no : 2



Occurrence of hypothyroidism according to age

Chart no : 3



Occurrence of hypothyroidism according to pattern of radiotherapy

DISCUSSION:

Hypothyroidism after Radiotherapy for Head and Neck cancer may adversely affect the quality of life of cancer survivors therefore the National Comprehensive Cancer Network (NCCN) recommends that thyroid function tests should be repeated every 6–12 months after RT for neck. But the clinicians often fail to assess routine thyroid function test before and after RT.

First case of hypothyroidism was reported in 1961 by Felix et al, in a patient of laryngeal carcinoma after six years of treatment with external Radiotherapy[2]. 41 patients of carcinoma larynx and hypopharynx treated with RT were followed up for ten years by Einhorn and Wikholm and noted 7.3% of hypothyroidism[3]. Weissler and Berry reported hypothyroidism after RT in 57% of his patients, similarly Leining et.al reported hypothyroidism in 26% of his patients[4,5]. In a study by Mercado *et al.*, with a median follow up of 4.4 years, reported hypothyroidism after radiotherapy in 48% of patients[6]. The documented incidence of hypothyroidism after RT varies between 3% and 44%. Most investigators have reported an incidence of 20-30% of hypothyroidism after radiotherapy.

In our study, the age group of patients varied from 30 to 75 years (mean - 55.58 years). Mean age of men was higher (61.51 years) as compared

with women (60.25 years).46 (92%) were males and four (8%) were females. These patient characteristics were similar to other studies published [7,8].

In majority of cancers,the primary site was hypopharynx(26%). Among the patients who developed hypothyroidism, 4(8%) were of glottic Ca and 4(8%) were of hypopharyngeal Ca. The primary site of the tumor was not a significant factor. The primary site varies in literature. According to Aich et al study, majority of cancers were seemed to arise from the Larynx (49%)[8].

Several mechanisms of injury to the thyroid have been proposed ranging from vascular or immunologically mediated damage to prevention of cell division leading to direct follicular destruction of the thyroid gland [8]. Fajardo et al.[9] have stated that damage to endothelial cells in thyroid capillary networks may be an important mechanism in both early and delayed radiation damage. Hellman et al, has reported that acute effects of RT depends on the balance between cell killing and compensatory replication of stem and proliferative cells. The development of late effects is due to the limited proliferative capacity of the stem cells affected by RT[10].

In our study, the follow-up period was 6 months post-RT, which is lower than the majority of studies. Tell et al and Turner et al had a mean follow up of 36 months and 21 months respectively [8,11].In our study 8 of 50(16%) patients develop hypothyroidism at six month follow-up, which is statistically significant with a P value of 0.022.In our study, the earliest follow up was done at 3 weeks post RT. The earliest follow up by Aich et al was at 6 weeks post RT, but noticed hypothyroidism (4.2%) at 12 months and not earlier[8].In our study the incident rate is high when compared to other studies. The documented incidence of hypothyroidism after RT varies between 3% and 44%.

In our study, 8% of the patients developing clinical hypothyroidism were between the age groups of 41 to 60 years. Hancock *et al.* observed that the relative risk of hypothyroidism decreased by a factor of 0.99 with each additional year of age but Colevas *et al.* observed that there was an increased incidence in patients with age more than 60 years [12,13]. In our study, the occurrence of hypothyroidism was higher in the elder age group as compared with the younger; however, the mean patient age groups analyzed were also in the range of 61 years. In our study only male patients developed hypothyroidism. In our study 92% were males and 8% were females so there was a higher occurrence of hypothyroidism in male patients.On the contrary Posner et al and hancock et al observed an increased occurrence of hypothyroidism in female patients [12, 14].

31 patents (62%) patients received chemotherapy either concurrent (16 patients) or neoadjuvant (15 patient) and 19 (38%) patients received RT alone. Turner et al (77%) and Mercedo et al (50%) had a very high number of patients receiving chemotherapy. These studies had a higher percentage of patients with locally advanced disease similar to our study. The occurrence of hypothyroidism was equal (8%) both in patients who received chemotherapy and in patients who did not. This was not statistically significant which was supported by studies of Mercado *et al.*, Turner *et al.*, and Koc et al[6,11,15].on the contrary in Aich et al study occurrence of hypothyroidism with the addition of chemotherapy was 21% as compared with 16.6% RT alone[8].

CONCLUSION:-

Hypothyroidism can occur as early as 6 months following RT.

Patients receiving both lateral and central neck radiation are more prone for Hypothyroidism.

Thyroid function tests should be made routine prior RT and during follow up period as early as 6 months and carried out lifelong.

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