A prospective study to determine the occurrence of hypothyroidism following treatment with radiation therapy in patients of head and neck carcinomas and factors influencing this

Dissertation submitted for the M.D. Degree (Br. IX- Radiotherapy) Examinations of the Tamil Nadu Dr.M.G.R. Medical University, to be held in April 2011

CERTIFICATE

This is to certify that **"A prospective study to determine the occurrence of hypothyroidism following treatment with radiation therapy in patients of head and neck carcinomas and factors influencing this"** is an original work by **Dr. Suparna Kanti Pal** in partial fulfilment towards M.D. Radiotherapy (Branch IX) Degree examination of The Tamil Nadu Dr. M.G.R. Medical University to be held in April 2011.

GUIDE _____

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A prospective study to determine the occurrence of hypothyroidism following treatment with radiation therapy in patients of head and neck carcinomas and factors influencing this

Aims of the study

Aims of the study: -

1. To determine the incidence of clinical and subclinical hypothyroidism in patients undergoing radiation therapy for head and neck carcinomas
2. To determine the factors influencing the occurrence of hypothyroidism
3. To evaluate impact on quality of life

Introduction

Introduction -

Head and neck malignancies are one of the most common malignancies in world and India. A vast majority of patients of head and neck malignancies are treated with radiotherapy. There has been evidence that such radiation to the neck may result in post radiotherapy hypothyroidism. The incidence of post radiotherapy hypothyroidism in as reported in various literature varies from as low as 6% (1) to as high as 68% (2) However, there is considerable debate regarding the incidence, influencing factors responsible, relationship with dose and time of development of the same. The available data for Indian patients, as found by Aich et al shows an incidence of 0.57% at 6 weeks and 21.8% at two years (3). Biochemical investigations are available for determination of hypothyroidism and supplementation with exogenous thyroxin is possible. Hypothyroidism manifests as fatigue, poor appetite, and temper fluctuation, leading to inability to meet social and familial roles. They also do effect on the professional and economic productivity of the patient and the family. This adds to the financial strain that results from the cost of care and loss of work days during the treatment period. Hypothyroidism also results in long term complications with respect to cardiac and general morbidity. Such morbidity in cancer survivors can be of immense physical, emotional, social and economic problems. Thus early detection and treatment of post radiotherapy hypothyroidism can result in avoidance of such complications and help in improving the quality of life. Most of the guidelines have been developed on basis of the western data. The applicability of the same, to Indian population, is not well defined, especially, in view of heterogeneity of data, originating from different population of the world. This not only includes the incidence but also time of occurrence of hypothyroidism post radiotherapy. This study is an endeavor to determine the incidence, associated factors in

development of hypothyroidism including the temporal association of the incidence with respect to the population from the Indian subcontinent.

Literature review

Carcinoma of the head & neck region is the commonest malignancy among Indian males, as per ICMR reports (4).

Sites of head and neck malignancies:

Carcinomas of the head and neck region, generally refers to the malignancies of the following sites:-

1. Nasopharynx [ICD-O-3:C 11]
2. Nasal cavity and middle ear [ICD-O-3:C30]
3. Accessory sinuses [ICD-O-3:C31]
4. Lip and Oral cavity [ICD-O-3:C00-08]
5. Tonsils and Oropharynx[ICD-O-3:C09-10]
6. Piryform sinus and Hypopharynx [ICD-O-3:C12-13]
7. Other and ill-defined sites in the lip, oral cavity and pharynx [ICD-O-3:C14]
8. Larynx [ICD-O-3:C32]
9. Carcinoma unknown primary with secondary neck nodes [ICD-O-3:C77.0]

Incidence and prevalence:

Malignancies of the head and neck sites are leading sites in all the cancer registries in India as per the consolidated report of the population based cancer registries(5). The estimated Age standardised incidence Rate (ASR) of head and neck cancers per 100,000 populations in India is one of the highest. The ASR for Indian males is 19.6 compared to the global average of 10.4, and Indian females 7.2 compared to 4.2 as per the GLOBANCAN 2008(6) database of the

IARC-WHO (International Agency for Research on Cancer- World Health Organization). Indian cities (Bhopal) have the highest incidence of oral malignancies in the world (7).

The major reason for such prevalence of head and neck malignancies is generally attributed to the use of tobacco, especially smokeless tobacco which is highly prevalent in India. 33% of the tobacco consumed in India is of smokeless variety (8), whereas in the west 85% of the tobacco is used in production of cigarettes alone. India is the third largest producer of tobacco in the world with an annual production of about 725 million kg (9) as per the Tobacco Board; Government of India. It is in excess of the estimated tobacco production by FAO (10) which was 685 million kg by 2010. The National household survey for Drug and Alcohol abuse in India reported, massive, 55.8% tobacco users, among males of the age group of 12-60 years (11). External beam radiation is an important tool for the treatment of Head & neck malignancy either alone or in combination with surgery and chemotherapy.

Thyroid gland

Thyroid gland is an endocrine gland situated in the anterior neck. It extends superiorly from the laryngeal prominence, inferiorly up to about 4 cm below the cricoid cartilage extending laterally about 3.25 cm bilaterally from the midline.(12) Due to its position it is nearly always irradiated while the neck is being irradiated for any head and neck malignancies.

Thyroid hormone:

The primary function of the thyroid gland is to produce thyroid hormones which include thyroxin (3,5,3′,5′-tetraiodothyronine) and 3,5,3′-triiodothyronine.

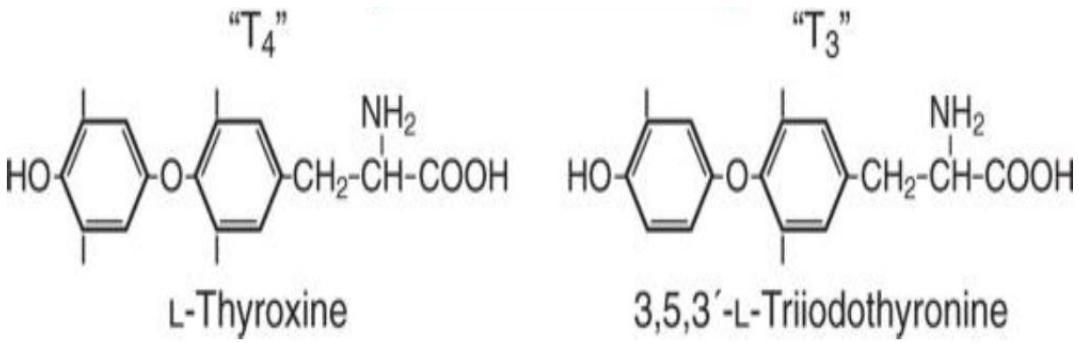

Fig-2.1: structure of T3 and T4(13)

The thyroid gland through a membrane glycoprotein called the *sodium-iodide symporter (NIS or SLC5A)* concentrates iodine from the plasma (14). This process is an active symport of the Iodine through the membrane against the gradient. This process is known as iodine tapping. Moreover, the iodotyrosine dehalogenase (Dhal) enzymes, also generates intracellular iodide resulting in increased iodide concentration in the thyroid gland (13).

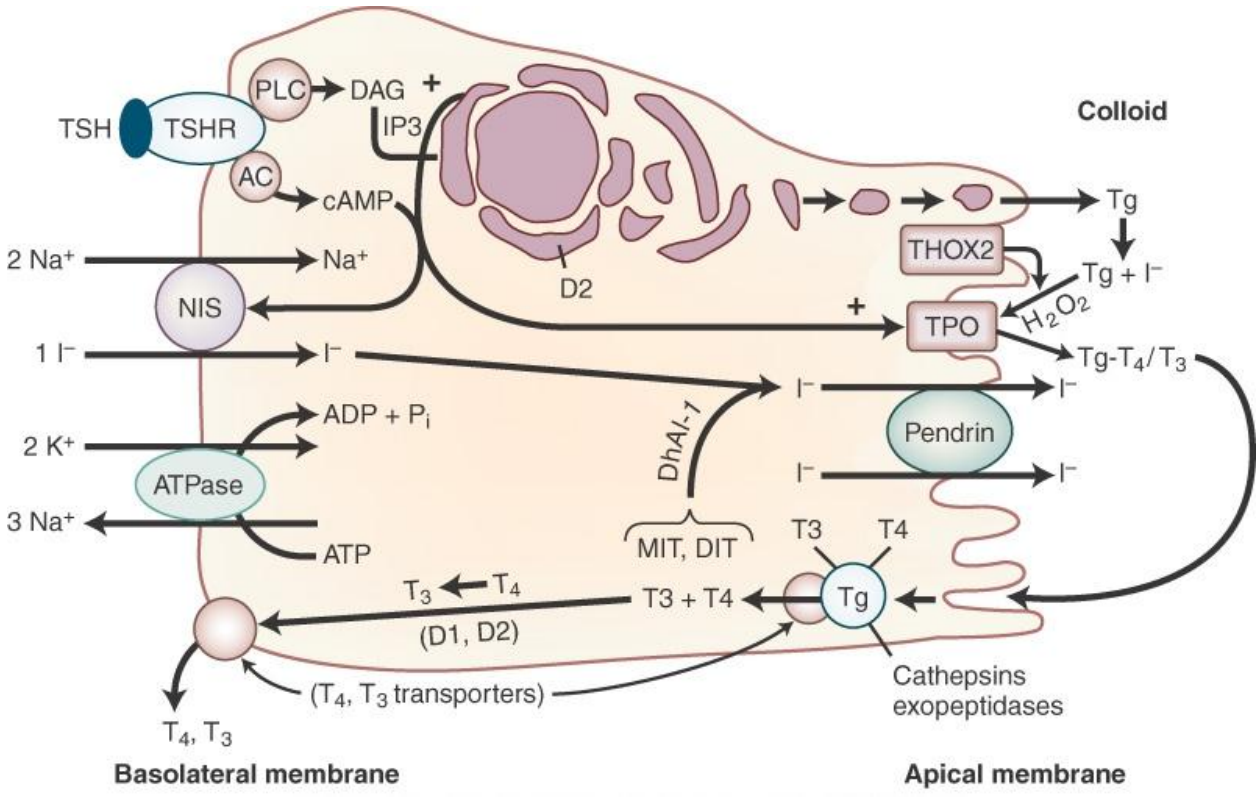

Fig-2.2 synthesis of the thyroid hormones (13)

The iodide is then oxidized and organified. The process of organificantion results in incorporation of oxidized iodide in hormonally inactive iodotyrosines MIT and DIT [Mono-iodo- tyrosine and Di-iodo-tyrosine]. TPO (tyrosine per-oxidase) catalyses the fusion of two molecules of TG bound DIT to result in formation of T4 and the fusion of MIT with DIT results in formation of T3. This reaction is called a coupling reaction. The thyroid hormones so formed are stored in the cells of thyroid glands and are released in the blood.

The thyroid hormones belong to the group I hormones which act on the intercellular receptors (15). These receptors are known as thyroid receptors (TR). The hormone receptor complex so formed attaches itself to the DNA via a zinc finger motif and exerts its physiological effects.(16)

The thyroid hormones have a wide range of physiological function. It increases the metabolic activity and oxygen consumption in most of the tissues except brain, heart, testis and retina. Thus it is calorie genic. On heart it is both inotropic and cronotropic,. It is pro developmental in the brain and the neural tissues, has catabolic effect on the adipose tissue. It increases the metabolism in Gastro-intestinal tract and the lipose tissue. (17)

Hypothyroidism and types:

Hypothyroidism is deficiency of the thyroid hormones either due to lesser production of the thyroid hormones or end organ resistance to it. This was first described by Gull in 1874.(18). Hypothyroidism is caused due to either impaired functioning of the thyroid gland, or due to impaired stimulation of the thyroid gland due to low levels of thyroid stimulating hormones. The lesser production of the hormones by the thyroid gland itself despite adequate amount of TSH is termed as primary hypothyroidism. The insufficient stimulation of the thyroid gland can be a result of the malfunctioning of the pituitary or hypothalamus or due to defects in the thyroid stimulating hormones (TSH) molecules. (19)

Primary hypothyroidism has been divided into clinical and subclinical hypothyroidism. This division is not based on presence or absence of the clinical features of hypothyroidism. Subclinical hypothyroidism has been defined as patients with elevated TSH levels with normal or low normal free T4 levels (20). It has been also described as preclinical hypothyroidism, mild hypothyroidism, early thyroid failure, and decreased thyroid reserve by various authors (20). Though called subclinical it may be associated with clinical symptoms or signs those akin to clinical hypothyroidism (21)

Historical perspective of hypothyroidism:

Hypothyroidism has been documented to be of common occurrence in the post RT period. Grover in 1929(22) was the first to suggest decrease in thyroid function following exposure to radiation. Felix et al (23) was one of firsts to document hypothyroidism in head and neck malignancies (carcinoma larynx) treated with radiation therapy.

Reasons of development of post radiotherapy hypothyroidism:

The reasons of development of hypothyroidism in such patients has been documented as follows-

1. Direct radiation damage
2. Small vessel damage Fibrosis of capsule (24)(25)
3. Relative ischemia due to RT induced carotid artery atherosclerosis(26)
4. Relative ischemia due to RT induced carotid artery atherosclerosis(25)
5. Change in size of the thyroid gland(25)
6. Development of anti-thyroid antibodies(27)

Incidence – World and India:

The incidence reported in literature is very varied. Most of the information that is available is western data based on Caucasian and Afro- American patients. Data from a few Indian studies is available. As it is noted in western literature, the incidence and severity varies between Caucasians and Afro-Americans (28) the western data may not be applicable to the Indian scenario. Incidence including India

Prevalence of hypothyroidism in general population:

The incidence of hypothyroidism in India has been found to be more compared to that of western population. A cross sectional study conducted in Chennai by Shantha et al(29) showed an incidence of 8.8% of hypothyroid patients in groups who were otherwise healthy[i.e., no features of Metabolic syndrome].

Incidence of hypothyroidism in post radiotherapy patients:

The incidences of hypothyroidism after radiotherapy for head and neck malignancies as documented in some of the literature are as follows:-

Table- 2.1-

Incidence of hypothyroidism after radiotherapy for head and neck malignancies

Author	Published in	incidence
Alkan et al 2008(30)	*Otlolaryngol Head neck surg* 139,787-91	49.3%
O cetinayak 2008 (31)	*Tumori 94:19*	40%
Bhandare et al 2007 (32)	*Int J Radiat Oncol Biol Phys* 64,4.1131-1139	29%-subclinical 32%(clinical)
Alterio et al 2007(33)	*Int J Radiat Oncol Biol Phys* 67, 1. 144-150	26%
Tell et al 2004(34)	*Int J Radiat Oncol Biol Phys* 60, 2. 395-400	17%(overt)
Mercado et al 2001(28)	*Cancer 92: 2892-7*	48%
Sinad et al 2000(35)	*Arch otlolaryngol head neck surg* - 126, 652-57	14.6%
Turner et al 1995(36)	*Int J Radiat Oncol Biol Phys* 31, 2. 279-283	23.8%

Cannon et al 1994 (24)	*Laryngoscope-104*	15%
Tami et al 1992 (2)	*Am j Otol* -13	45-68%
Hancock et al 1991 (37)	*N eng J med* 1991 325: 599-605	47%
Buisset et al 1991 (38)	*Ame j o surg* 162;345-347	34%
Lening et al 1990(39)	*Otlolaryngol Head neck surg* -13	6-28%
Posner et al 1984 (40)	*Laryngoscope 94*	37%
Tamura et al 1981 (41)	*Cancer 47(11): 2704-11*	26%
Estefan et al 2009 (42)	Acta Otorrinolaringol Esp.2009;60(4):268-271	36.4%

Post radiotherapy hypothyroidism In Indian Patients:

Data regarding the incidence in Indian patients are mostly from those undergoing conventional irradiation. Available Indian data for conventional radiotherapy shows 17.8 % and 21.8 % were found to have clinical and sub-clinical hypothyroidism at two year (3) , about 3.6% at 6 months and 0.57 % at 6 weeks. Moreover routine evaluation of TSH and TFT has not been started on a regular basis in India.

Unpublished data presented in AROI TN CON 2009 by Dr. T Sujit et al (43) showed an overall incidence of 20% at 12 months with a mean duration of onset at 7.2 months (range 4.3 to 9.7 months).

Regarding our patients who are treated in our institute, there is no prospective data regarding the occurrence of hypothyroidism. In early 1990's Dr.Jaylakshmi (44) (thesis no D825 CMC Vellore DODD library -1992) had done a retrospective study on development of hypothyroidism in patients receiving radiation therapy to neck for any cause including lymphoma, by conventional planning only with 100% of the thyroid volume within the irradiated fields. It showed an incidence of 16% on long term follow up. Being a retrospective study the onset of the thyroid dysfunction could not be determined.

However the study is limited by the fact that a lot of patients today receive conformal radiotherapy and the radiation fields may not be including the whole of the thyroid gland or that the whole of the thyroid gland may not be irradiated with uniform dosage. Most of our patients today who receive radiation to the neck belong to the subgroup of carcinomas and not lymphomas (66% of the patients were lymphoma patients treated with mantle field irradiation in that study). (44)

Time for development of hypothyroidism

The time to development of hypothyroidism has varied across the studies. It has ranged from weeks to years. However, most patients developed the problem in months. Alkan et al (30) showed the average duration of onset was at 6.08 months and 83 % of the patients who developed hypothyroidism developed within 9 months.

Nishiyama et al (45) has described significant rise since 4th month and 6th month from starting of radiotherapy (~4.5 months from completion of RT). The mean TSH was 7.57 (compared to the baseline TSH of 1.53(+/-1.01) mU/ml). The elevation was noted in 17 out of 22 patients, and was statistically significant (P=0.003). This increase of TSH was much earlier than those found in the western literature.

Available Indian data by Aich et al (3) showed an incidence of 0.57% at 6 weeks post radiotherapy 3.6% at 6 months post radiotherapy.

Sinad et al (35) found the average time of development of hypothyroidism to be about 8.2 months (with a range of 1-21 months). In 83% of the cases it was evident by 12 months. However some patients may become hypothyroid even after years of treatment.

Most of the other western studies [with American and European population] have looked into the long term consequences and have found that the onset of hypothyroidism can occur even decades after the treatment with radiation therapy to head and neck region.

Turner et al (36) commented that there is no clear correlation between the degree of thyroid dysfunction and time from radiation & that it may occur, early following treatment.

Role of co-factors in development of hypothyroidism:

Age-

The relationship with development of post radiotherapy hypothyroidism has been found to be inconclusive. Hancock et al (37) had shown that the chance of development of hypothyroidism is more in the younger and paediatric age group.

Sex-

Female sex has been found to be a significant co-factor in development of hypothyroidism by some researchers (30)(37) and (40). However other authors have shown that there were no statistically significant difference between the event and female sex. Aich et al (3) in his study among the Indian patients did not find any significant difference.

Chemotherapy-

Though chemotherapy has been much mentioned as a probable additional factor for toxicity, a lot of literature did not support a difference in development of hypothyroidism. However, in his study by Kurten (46) et al showed that patients who receive chemotherapy for Hodgkin's' Disease has a lower threshold for developing hypothyroidism (<40Gy). The Indian study by Aich et al (3) did not show any relation with administration of neo-adjuvant or concurrent chemotherapy.

Smokers:-

There is no conclusive evidence that smoking affect the incidence of hypothyroidism. However some argue that smoking might aggravate the vessel damage leading to hypothyroidism in post RT patients.

Surgery: -

Alterio et al (33) did not find any difference in occurrence of post RT hypothyroidism in patients who had undergone surgery compared to those who have not. On the contrary Turner et al(36) (P<.001) Gande c (47) P=.003 and Posner et al(40) (incidence of hypothyroidism was 43% vs. 30%) did find neck surgery to be of significant influence for development of post radiotherapy hypothyroidism. Smith et al (48) in their population based study of older patients (> 65 years at the time of onset of disease) found that there is no significant statistical difference in development of hypothyroidism in patients treated with RT alone VS., RT and surgery. (P=0.15). Though it clearly showed a significant increase in incidence of hypothyroidism in between patients treated with RT and surgery VS., Surgery alone (p<.001) and RT alone VS., surgery alone. (p<.001). In his study, neck dissection was not a modifying factor for incidence of hypothyroidism. There has been some evidence to show that the type of neck surgery patients undergo does affect the incidence of development of hypothyroidism. Tami et al (2) in his study did find a significant difference between the incidence of hypothyroidism in patients who had undergone neck surgery [45% those who had undergone (surgery compared to 29% in patients who did not have any surgery.]. On subset analysis, the patients who did not have any laryngectomy during surgery were found to have an incidence of 28% suggesting that surgery involving laryngectomy is a factor in development of post RT hypothyroidism. Cetinayak et al (31) in his study has shown that there is no role for neck dissection in development for hypothyroidism but for surgeries involving thyroid gland.

Sinard et al (35) in their study had found that non laryngeal surgery does not change the incidence of development of hypothyroidism as in neck dissection. Even with partial laryngectomy, there is no change in incidence. Patients who had undergone total

laryngectomy with thyroid lobectomy, the incidence is much higher at 61% compared to 48% in patients who did not have any surgery (P<.001).

Relationship with radiotherapy dose and volume: -

Being a parallel organ, thyroid dysfunction depends both on the volume and dose of irradiation. Different studies have explored the option of tolerance dose of the thyroid and the volume. However the relationship is yet to be definitely established (49). Emami et al (50) had noted, tolerance values of 8/5, 13/5, and 35/5, i.e. incidence of clinical hypothyroidism respectively in 8%, 13%, and 35% of patients after 5yrs of radiation therapy when the dose received are 45 Gy, 60 Gy, and 70 Gy respectively. However, this data does not give us any idea with relation of the volume of thyroid gland irradiated and is therefore valid only when the whole of the thyroid gland is within the field of radiation and is uniformly irradiated, which is not the case in most of the modern era of conformal radiation and IMRT. Hancock et al (37) in their study has shown that the risk of developing increases to 40 % in patients receiving >30 Gy compared to 12% for patients receiving less than that. In a study by Kurten et al(46) the authors showed that there is a similar rise of risk from 27% for patients receiving a dose lesser than 45 Gy compared to 40 % for doses >45 Gy.

Including the thyroid in the low-neck field to 50 Gy results in hypothyroidism in 30% to 50% of patients at 5 years, was found in a study by Norris AA et al(51), suggesting that the threshold for this complication is <50 Gy.

Alkan et al (30) had shown in their study that dose received by the whole of the thyroid gland is a significant risk factor. The dose received to the whole of the thyroid gland in their study was 6.07 +/- 35 Gy in the patients who had developed hypothyroidism was significantly

higher than the group who remained euthyroid, which was 5.92 Gy +/-25 Gy ($p<.05$).

Bhandare et al (32) the incidence of hypothyroidism increases by 16 % for doses more than 45 Gy.

The study noted that if the treated volume >=85%then the chance of developing clinical hypothyroidism was 23% compared to 0% when the treated volume is < 50 %. The incidence of subclinical hypothyroidism was 25 % and 10% for bilateral and unilateral neck nodes irradiation respectively.

Using Dose Volume Histogram (further referred as DVH), Alterio et al (33) did not find any relationship between the irradiated thyroid volume and dose, with respect to V10, V30, and V50. When V10, V30, V50 are thyroid volumes irradiated by a dose of over 10, 30 and 50 Gy respectively. As per the authors however, the scope of use of DVH in their study was limited by the act that the study cohort had a relatively uniform DVH. Yoden et al (52) in their study found V10-60 (percentage of volume of thyroid gland receiving radiation doses between 10 Gy and 60 Gy) to be a possible risk factor. They also reported that V30 (percentage of volume receiving > 30 Gy) was a predictor of peripheral hypothyroidism. It was also found to be a significantly correlating with peak serum TSH levels.

Presentation of radiation induced hypothyroidism-

The general features of hypothyroidism include depression, lethargy, early fatigability, general malaise, anhedonia, dry skin, constipation. (42), (27). Due to concomitant presence of such events in cancer survivors, they often tend to get looked over. (27)This is more in cases of patients belonging to the weaker socio-economic status where such symptoms are generally attributed to the prevalent social condition and or loss of economic security. Moreover, due to these confounding symptoms relaying on clinical examination for detection of post radiotherapy hypothyroidism may not always be useful (27). However, these symptoms are important from the perspective of the patient and his or her family members as they impair the quality of life and prevent rehabilitation of the patient and the family not only from the view of health but also from the view of economic rehabilitation and social reintegration of the patient and the family. The first because of loss of economic productivity and the later by prolonging and reinforcing the stigma associated with cancer survivorship.

Treatment and Quality of life:

Thus hypothyroidism does affect quality of life **(QOL)** in cancer patients and cancer survivors, to whom it matters the most. However it can be easily treated by exogenous supplementation of thyroxin at low cost. The cost of thyroxin supplement of 100 mg per day entails a retail cost ranging from ₹ 0.80 to ₹ 1.26 per day depending on the manufacturer. The bulk cost is even lower at ₹ 0.27 (53). Tests to detect hypothyroidism are available (TSH/ TFT) but are not routinely used in post radiotherapy patients in countries like India.

Exogenous supplementation of levothyroxine is required for clinical hypothyroidism.

Supplementation of levothyroxine improves the symptoms in the symptomatic patients who have subclinical hypothyroidism [i.e. Biochemical hypothyroidism]. Moreover, it has been shown that subclinical hypothyroidism causes cardiac dysfunction even when the patient is absolutely asymptomatic and supplementation of levothyroxine results in improvement of the same (54). The increased risk of coronary atherosclerotic disease has been documented in patients of subclinical hypothyroidism by some studies. These include the Rotterdam Study which showed significantly increased prevalence of aortic atherosclerosis and consequently myocardial infraction (55) in elderly female patients with subclinical hypothyroidism. Danese et al in their quantitative review of literature (56) showed that the treatment with levothyroxine supplementation results in lowering of mean serum total cholesterol and LDL cholesterol concentration. The Chrocrane review on supplementation of levothyroxine for sub-clinical hypothyroidism showed some evidence that such replacement improves some parameters of lipid profile and LVF (57).

Guidelines for post radiotherapy screening:

There is no standard universal guideline regarding the monitoring of thyroid function post radiotherapy. NCCN (58) recommends monitoring TSH and TFT in post RT patients treated with radiotherapy with head and neck malignancies every 6-12 months, in cases where the neck is irradiated. ESMO (59) recommends the same at 1 year, 2 year and at 5 years post radiation therapy. The ESTRO/TMH international symposium 2005(60) recommended monitoring of T3 T4 and TSH annually for post op patients particularly in patients with laryngeal malignancy. However, even in developed countries like Netherlands the most of the monitoring (75%) is done only when the patients complain of symptoms. In a nationwide survey carried out in Netherlands

by Galbo et al (61) biannual monitoring of TSH was done by only 24% of the physicians involved in the follow up care of the patients who had undergone radiotherapy for laryngeal carcinoma.

These guidelines (NCCN, ESMO etc.) are based on the western data; and the need in Indian patients might differ in terms of time and frequency of the monitoring. In our institution, we generally advise monitoring during the follow up period with TSH at each follow up, i.e., 6 weeks, 19 weeks, 32 weeks, 45 weeks and 58 weeks after completion of radiotherapy and thereafter every 6 months at the time of follow up.

Moreover, while ordering a test for monitoring in our patients, we always have to be aware of the resource constraints.

Data regarding Indian patients are scarce especially for those who undergo conformal radiation. There is need to know the incidence of hypothyroidism and the factors influencing the same. Such data can help us to identify the patients who need to be intensively followed up and judicious use of resources can be done.

Materials and method

Materials and methods

Study subjects-

Inclusion criteria:-

1. Adult patients[more than 18 years of age] with non-metastatic Head & Neck carcinoma, without any intracranial extension, of the following sites-
    a. Nasopharynx
    b. Sinonasal cavity
    c. Oropharynx
    d. Oral cavity
    e. Hypopharynx
    f. Larynx
    g. CUP [Carcinoma of unknown primary]
2. Patients receiving radiotherapy(>45 Gy) as part of treatment
3. Radiation field extending to lower neck , unilateral or bilateral
4. Performance score- 0 to 2

Exclusion criteria:-

1. Known to have hypothyroidism
    a) At the time of screening
    b) The history of hypothyroidism in the past, for which he/she is currently on supplements. [Hypothyroidism was defined as TSH more than the maximum of the normal range, or TSH >4.5 micro IU/ml].

2. Who has a history of previous exposure to radiation therapy in Head and neck region
3. Carcinomas with intracranial extension by clinical or radiological examination.

Target sample size calculation:-

Target sample size was calculated based on the following formula-

Required sample size= $4 PQ/ d^2$

When P= likely incidence, d= expected deviation from the incidence

Q= 100-P

Considering the incidence of hypothyroidism in post radiotherapy patients in Indian population be around 15 % and the range being around 5-25 % [i.e., deviation of about +/- 10 %]

P= 15

Q= 100-15=85

d= 10

So, calculated sample size= $(4 \times 15 \times 85)/ 10^2$

=5100/100 =51

Materials:-

1) Informed consent document English [annexure-2]
2) Translations of informed consent documents
    a. Tamil- annexure 3
    b. Hindi-annexure 4
    c. Bengali- annexure 5
3) Standard thyroid questionnaire –annexure 6
4) Thyroid questionnaire -2 [annexure 7]
5) Quality of life questionnaire –FACT H& N [annexure 8] (62)
6) Thrermolumisent dosimeter [TLD][fig-]
7) TLD holder [fig-]
8) Treatment machines- Theratron 780C[cobalt 60 tele-therapy machine –theratronics], Primus [Lenier accelerator –simens]
9) Simulator-
10) CT machine for CT in planning position [planning CT]- simens
11) Treatment planning system – Oncentra, Plato, Aria.

Methods:-

The patients who fulfills the above mentioned criteria , were explained about the aims, objectives, protocol, investigations, required for the study both verbally and by a written informed consent document, as approved by the institutional review board and ethics committee [hereafter referred as IRB] in a language patient can understand. Their doubts and queries, if any, answered. As and when required, help of translators, who are well versed with the present study, were taken.

After the informed consent is obtained, they were screened for any thyroid abnormalities. The screening tests include the followings:-

a. Blood for TSH
b. Blood for TFT [T4 and FTC]

They were also asked to fill up the following questionnaires':-

a. Standard thyroid questionnaire -1 (27)
b. Thyroid questionnaire -2[as generated by CMC]
c. Quality of life questionnaire- FACT H & N

Once they are found to be fitting into the euthyroid group by the blood tests. They were included as the part of the study. Patients, who were found to be hypothyroid on investigations, were not included in the study. They were referred to the Department of Endocrinology for further evaluation and necessary management.

The patients were started on treatment as required as per their treatment plan and modality of radiation chosen by the patients [conventional 2D cobalt, 3 DCRT, IMRT] with or without chemotherapy, with or without biological agents.

While on treatment the measurement of the point dose to the thyroid region was done. The points of measurements were based on the surface marking of the thyroid gland (12) as follows-

Isthmus-

i. A point in the midline, 1 cm below the arch of cricoid cartilage and a horizontal line of 1.5 cm is drawn across the trachea. This line represents the upper border of the isthmus.
ii. A second point 1.25 cm below the first is taken and a 1.5 cm horizontal line is drawn. This line represents the lower border of the isthmus.

Lateral lobes of the thyroid

i. A point is taken 1 cm below the lower border of the isthmus at the lateral most point.
ii. A point is placed 2.5 cm lateral of the point (i)
iii. A point is placed at the level of laryngeal prominence on the anterior border of the sternocledo mastoid. This point represents the upper pole of the thyroid gland.

The lateral end of the line representing the lower border of the isthmus is joined to point (i) and point (ii) is succession with the convexity of the line towards the caudal end. This would be representative of the lower pole of the thyroid gland. A line is used to join the upper pole and the upper border of isthmus in its lateral most aspect. Another line is used to join the lateral most point of the lower pole and the upper pole.

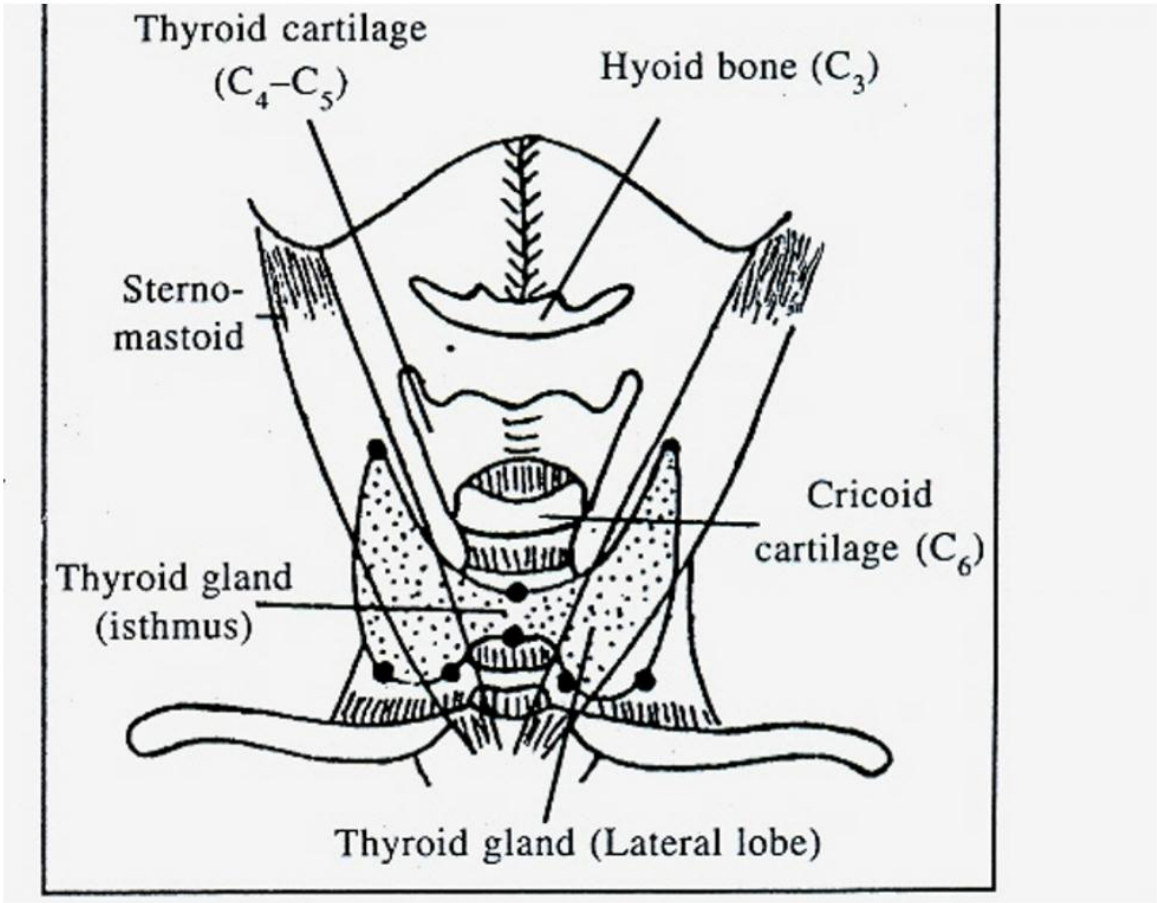

Fig-3: surface anatomy of the thyroid gland (12)

Based on this surface anatomy, the points for measurement of point dose to the thyroid were made. The points were as follows:-

i. A point 1 cm below the thyroid notch at the anterior border of the sternocledo mastoid muscle point 1(right) and point 2(left) to represent the right and the left upper poles of the thyroid.

ii. A point at midline, at the midpoint of the thyroid notch (laryngeal prominence) and sternal notch, representing the isthmus of the thyroid- point 3.

iii. A point 3 cm below the cricoid cartilage and 2 cm from the midline so as to represent the right (point 4) and left (point 5) lower poles.

The points are shown in the figure 2.

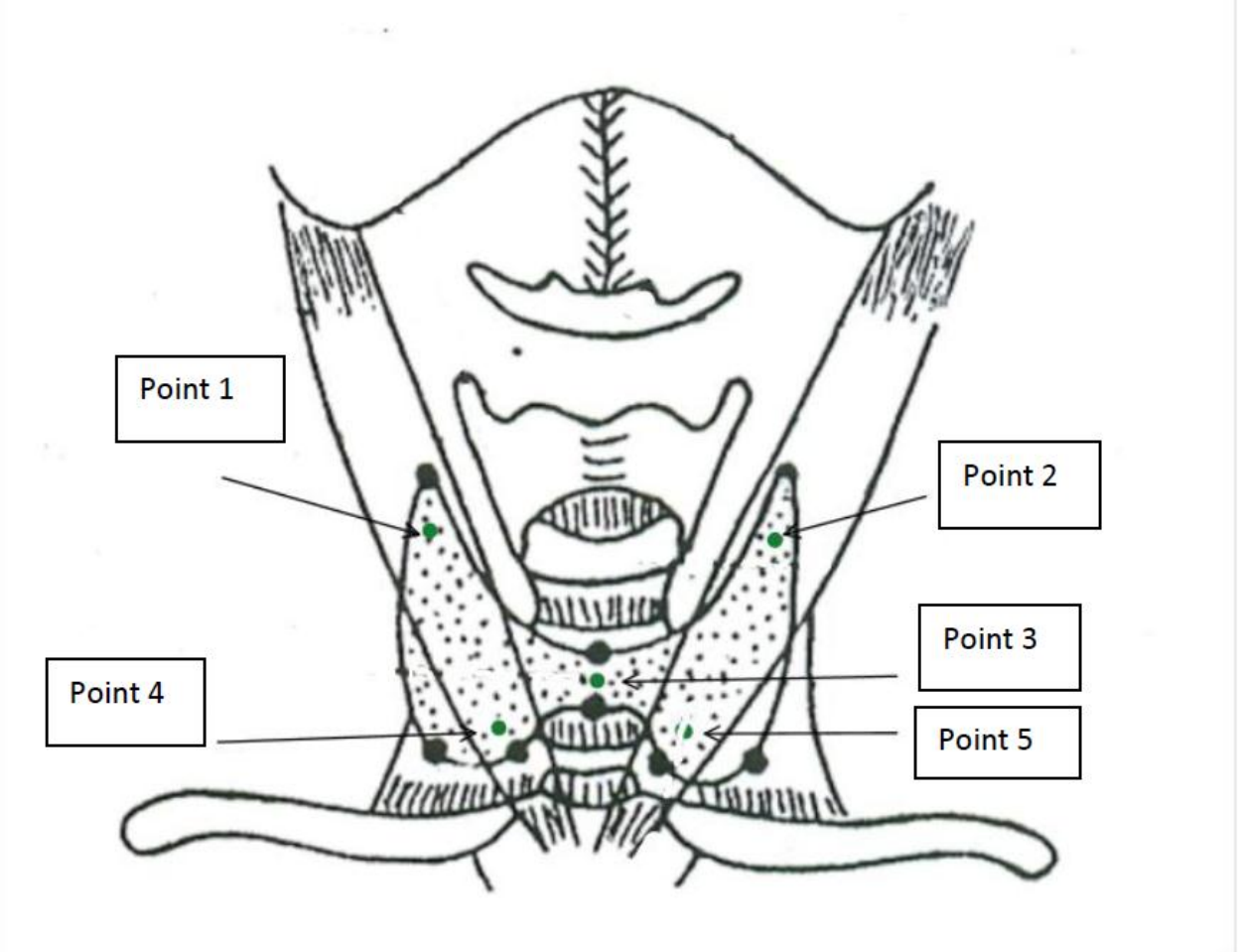

Fig-4: points for measurement of the point dose to the thyroid gland.

Fig- 5: longitudinal view of TLD holder

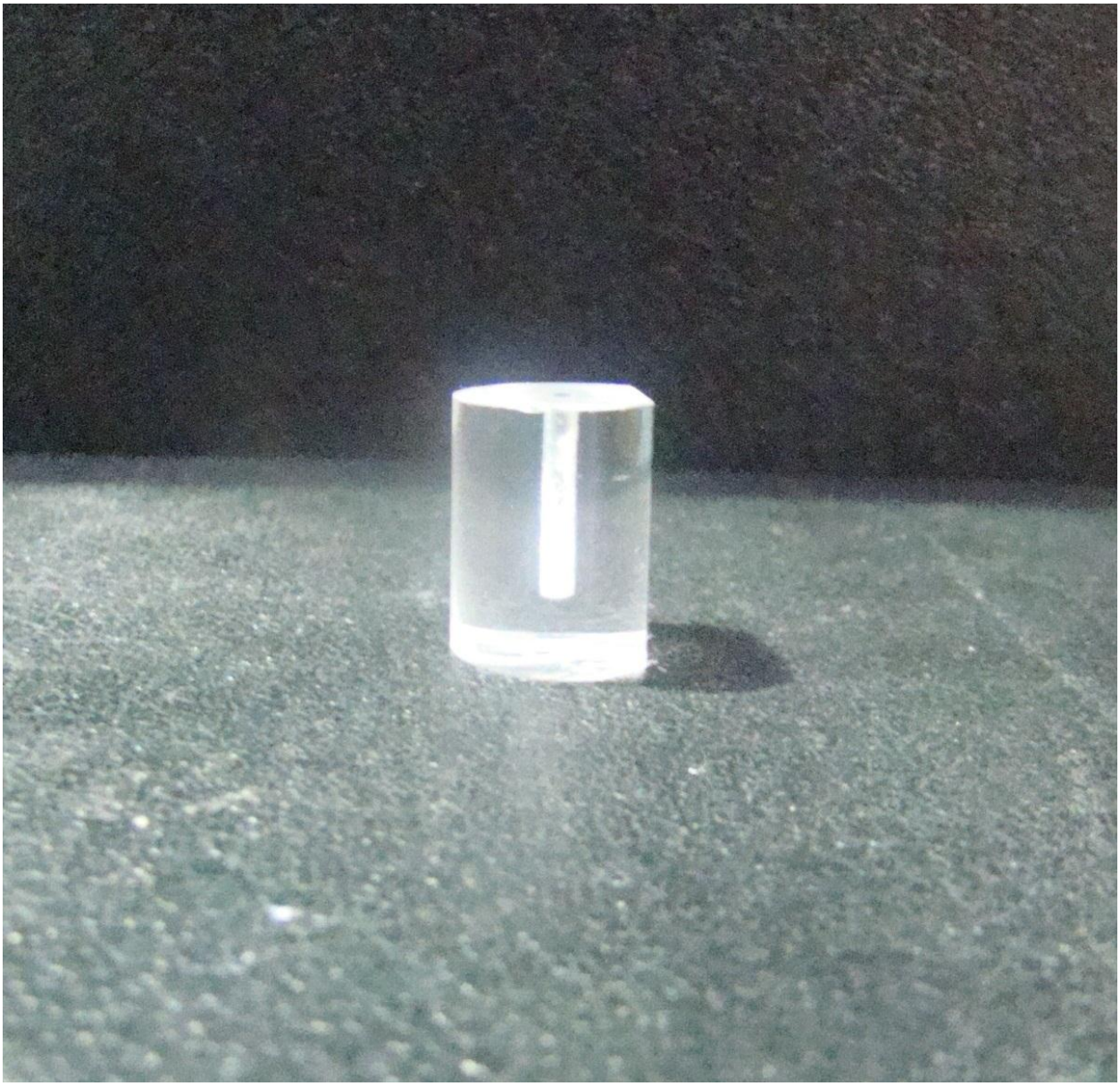

Fig 6- lateral view of the TLD holder

The measurements were done with the help of Thermoluminisent dosimeters (herein referred as TLD). The TLDs were placed in a specially placed TLD holder made of persplex. The holder is cylindrical in appearance with one side flattened so that the holder can be easily placed over the body or the ray cast of the patient. The dimension of the holder was 1 cm in diameter and 2 cm in length. A cylindrical hole is drilled at 0.5 cm from the flat surface along the axis of the holder so as to allow two TLD chips to hold snuggly in position. [Fig 3, 4]

The TLDs were calibrated and data generated for measurement.

At the end of RT the following assessment was done –

a. Standard thyroid questionnaire -1
b. Thyroid questionnaire -2 [as generated by CMC]
c. Quality of life questionnaire- FACT H & N
d. Clinical assessment of disease status

The patients were followed at the following time schedule

a. At 6 weeks form the date of completion of radiotherapy
b. At 18 weeks [4.5 months] from the date of completion of radiotherapy
c. At 30 weeks [7.5 months] from the date of completion of radiotherapy

An allowance of +/- 2 weeks in each follow up, to allow for any personal, physical, social, economic, or environmental inconvenience beyond the control of the patients. This was kept especially in view of the patients who come from the remote areas and distant places.

In cases the patient did not turn up within the specified limit, an attempt was made to contact the patient to ascertain the reason and the condition of the patient.

At these follow up the following were done:-

a. Standard thyroid questionnaire -1
b. Thyroid questionnaire -2 [as generated by CMC]
c. Quality of life questionnaire- FACT H & N
d. Assessment of disease status- clinical and radiological if necessary
e. Blood for TSH and TFT (FTC and T4).

Patients were then classified into groups as per their results of the blood tests. Hypothyroidism as defined biochemically or sub clinically as raised TSH only (normal-0.3 to4.5), or clinical hypothyroidism with raised TSH and a low T4 (normal- 4.5- 12.5), free T4 (.8 to 2).

TSH¬	T4 <4.5m g/dL or FTC<0.8	T4>4.5m g/dL and FTC>0.8
> 4.5m IU/ml	Clinical primary hypothyroidism	Subclinical primary hypothyroidism
<4.5m IU/ml	Central primary hypothyroidism	euthyroid

The thyroid questionnaire was given to the patient for self-administration with or without the help of the investigators. Both the standard and the generated questionnaires were in Likert scale. Likert scale is psychometric one-dimensional scaling method invented by Resnis Likert.(63). A 3 point scale was used for these questionnaires. The standard questionnaire was taken from the standard used by Galbo et al (27).

For the purpose of measurement of QOL, the FACT H & N questionnaire (62) was used. This is a standard questionnaire and had been used and validated by various investigators.(64)(65). This questionnaire was also based on Likert scale. This self-administered scale contained both subsets of questions for physical, emotional, functional, social wellbeing and a head and neck section. While calculating for the scores, the scores for the negative questions were subtracted from the maximum possible score (=4) before adding to the final scale.(66).

The results were then tabulated and analysed.

Results

Results

Screening data -

In the current prospective study 60 patients were screened. Out of these patients 7 patients did not fit into the eligibility criteria due to age [1 patient -1.67%], re irradiation [2 patient s-3.33%] and intracranial extension [4 patients -6.67%]. [Table-1]

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Table-5.1

TOTAL NO PATIENTS SCREENED

Total	60 [100%]
Pediatric age group	01[1.67%]
Re-irradiation	2[3.33%]
Intracranial extension	04[6.67%]
Eligible for screening tests	53[88.33%]

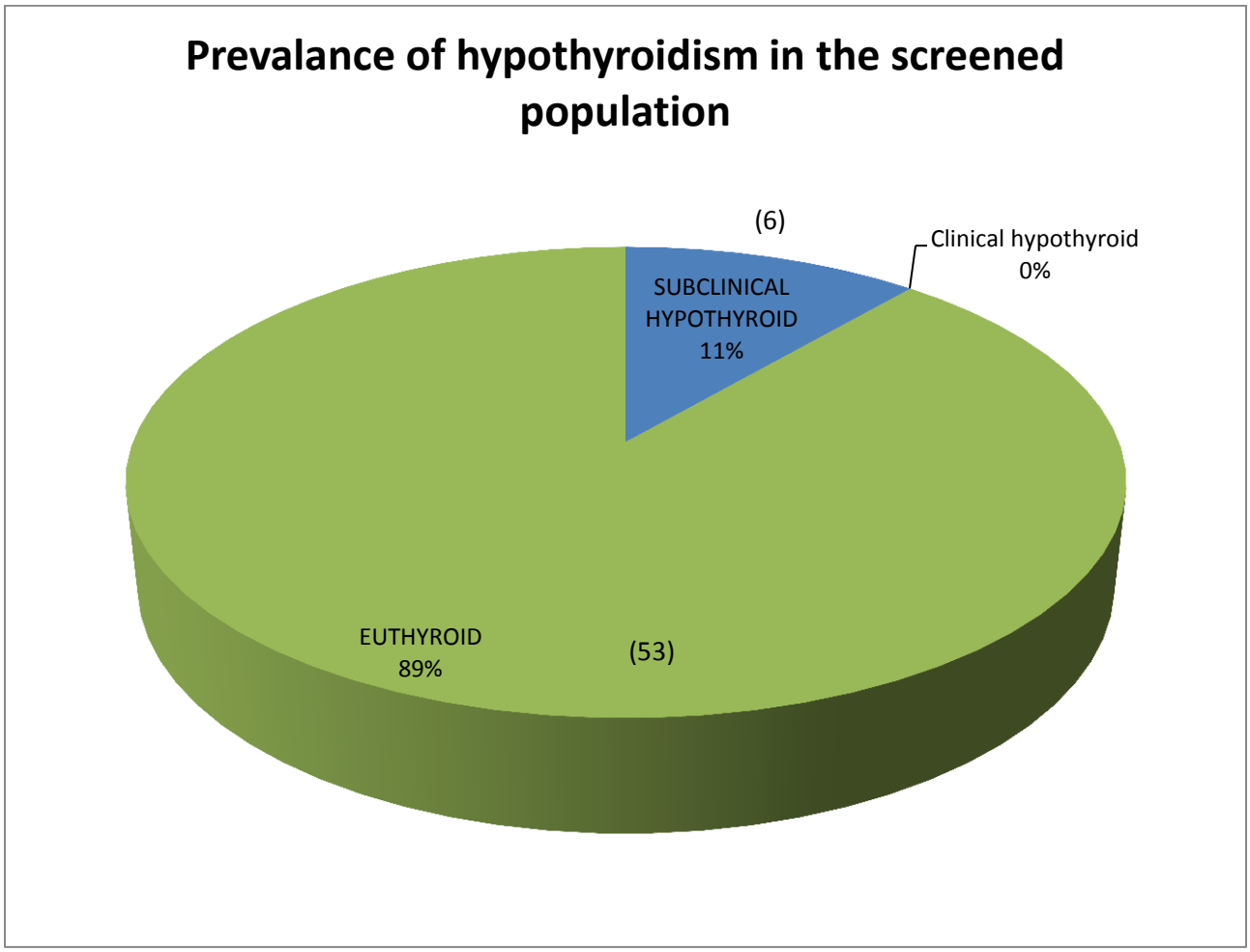
Table – 5.2

Prevalence of hypothyroidism among the screened patients

	Numbers	
Total	53[100%]	
Initial hypothyroid	Sub-clinical	6 [11%]
	Clinical	0
Initially euthyroid	47[88.68%]	

Out of those consented for screening for hypothyroidism, 6 patients or 11% were found to be hypothyroid. All the 6 patients had subclinical hypothyroidism based upon biochemical parameter (TSH, T4 and FTC). [Table 2: Screening data]. The rest [47 (88.68%)] were eligible for inclusion into the study

Figure:-5.1: prevalence of hypothyroidism in the screened population



Demographic parameters:

Age and Sex-

The age and sex distribution is showed in the table –3.

Table-5.3

Distribution of the study population according to age and sex

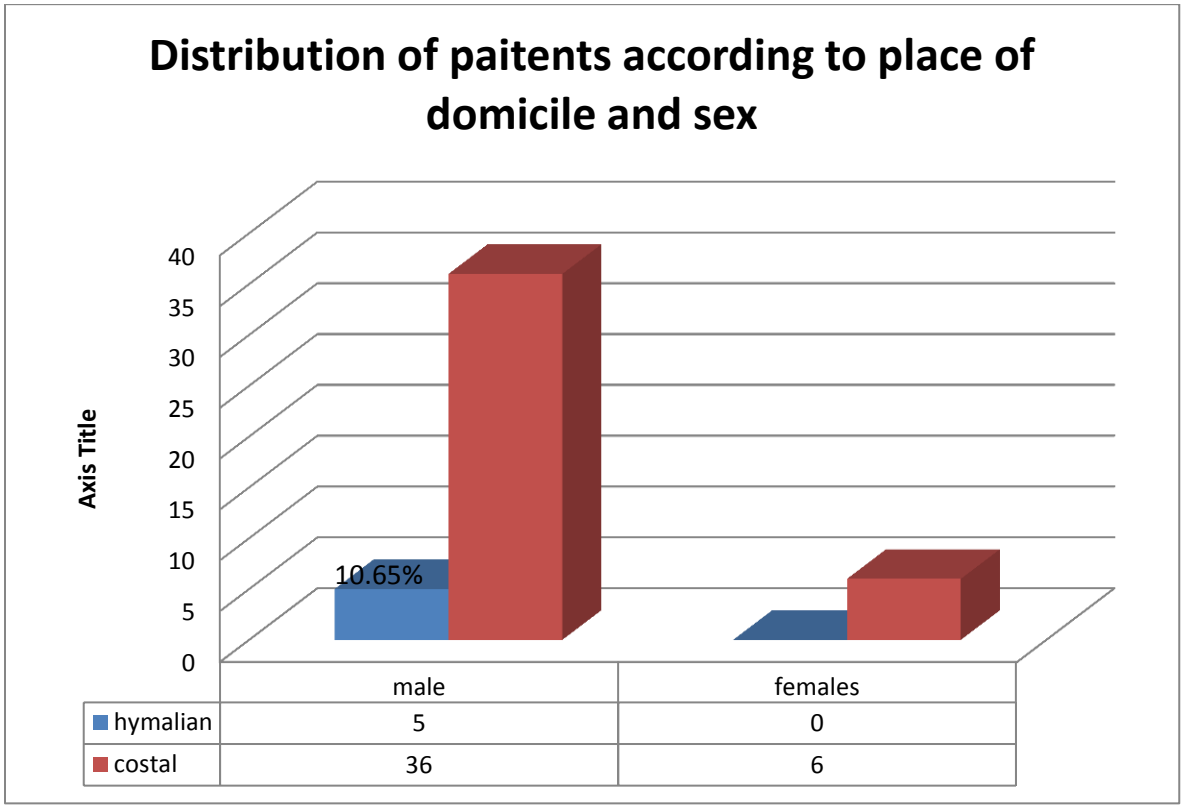
	Male	Female	Total
18-40	2[4.88%]	2[33.33%]	4[08.50%]
41-60	26[63.41%]	4[66.67%]	30[63.83%]
>60	13[31.70%]	0	13[26.66%]
Total	41[87.23%]	6[12.77%]	47[100%]

Among those enrolled in the study, There were 41 males and 6 females enrolled for the study. The males comprised of 87.23 % and females only 12.77 %. As per age group there were 30 patients[63.68%] belonged to the age group of 41 to 60 years, 13 patients were above 60 years [26.66%] and only 4 patients [8.5%] were lesser than 40 years of age.

Place of domicile-.

The study cohort was a mixed cohort of patients residing at the costal and Himalayan regions of India.

Fig-5.2:



Most of the patients were from the coastal region of India. There were 5 patients from the sub Himalayan region, which accounted for 10.65% of the study population

Addiction habits:-

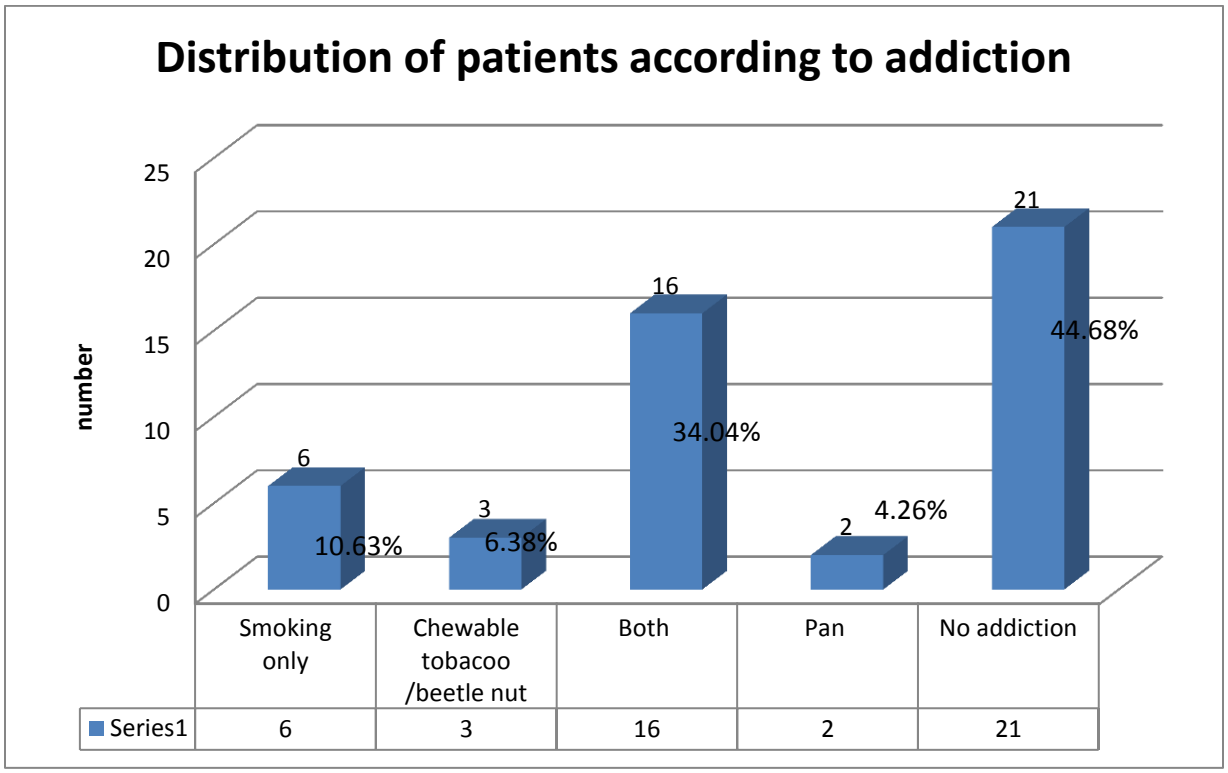
Data, regarding the addiction data was also collected and analysed.

Table-5.4: Addiction habits among the study population

Addiction type	Frequency	Percentage
Smoking only	6	10.64%
Chewable tobacco /beetle nut	3	06.38%
Both	16	34.04%
Pan	2	04.26%
No addiction	21	44.68%
Total population	47	100%

There were 20 [44.68%] patients in the study group who were smokers. They had however, quitted smoking after being diagnosed of having malignancy. 16 of them [34.04%] were also addicted to either chewable tobacco or beetle nut. In addition, another 2 patients were addicted to Pan [beetle leaf].

Fig-5.3: Distribution of patients according to sex



Comorbid factors:-

The co-morbid factor of hypertension and diabetes mellitus was recorded.

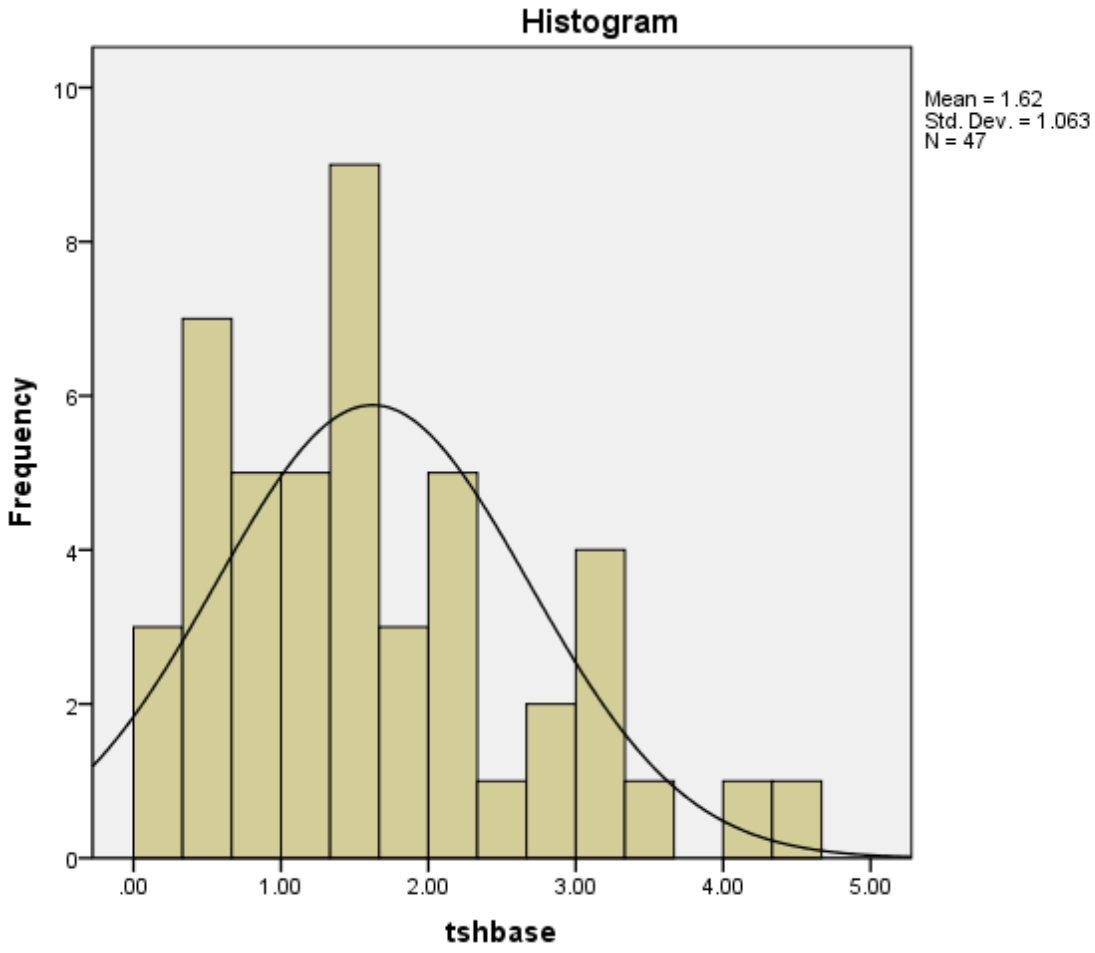
Table-5

Distribution of patients according to co-morbidities

	Yes	No	Total
Hypertension	6[12.77%]	41	47
DM	2[4.55%]	45	47

Among the 47 patients 6 patients [12.77%] had hypertension and were on treatment with anti-hypertensive, while 2 [4.55%] were diabetic and were on OHAs. None of the patients were on regular use of insulin in this study group.

Fig-5.4: baseline TSH levels plotted as histogram



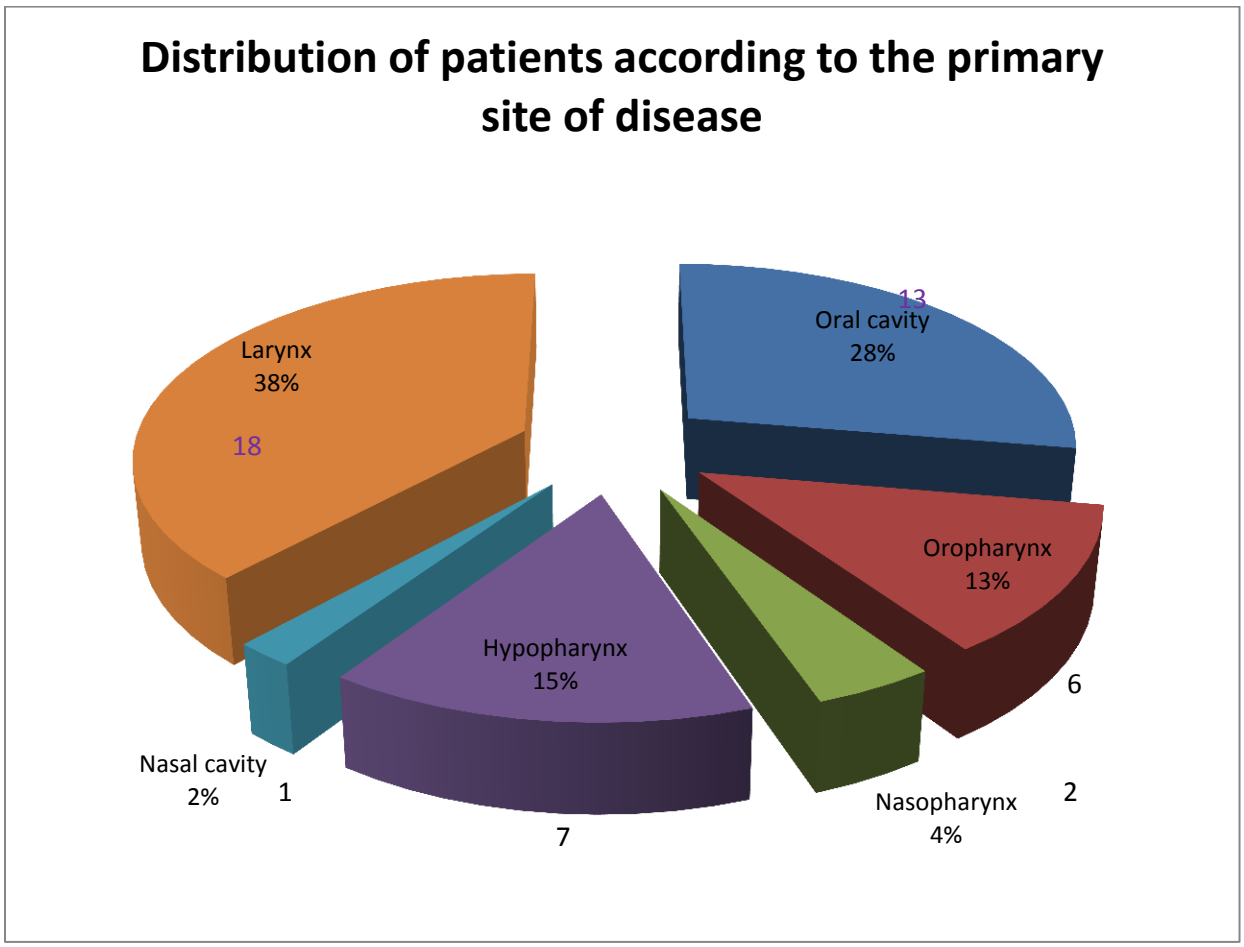
The baseline TSH data was plotted in form of histogram which showed a near normal distribution of the TSH values with mild skew to the left.

Disease characteristics:-

Site of the disease-

The patients in the present study were distributed across various sites of the head and neck malignancy.

Fig-5.5: Pie chart showing distribution of patients according to the primary site of disease.



Among the various sub-sites, larynx was the most common site with 38% [or, 13 patients] of the total study population. Oral cavity [13, 28%], Hypopharynx [7, 14.91%] and oropharynx [6, 13%] were the other commonly occurring site.

Stage of the disease with primary:-

Majority of the patients in the study group[31 out of 47] were of locally advanced nature with stage III and IVa, making up the 66% of all patients. It gives an indication that our patients present late in the course of disease.

Among the various disease sites, the patients with laryngeal carcinoma presented relatively early. 12 of the 18 patients of carcinoma larynx [66% of the patients] belonged to the stage I and II, in contrast to the rest of the sites where, only 4 out of 29, i.e. 13.8% belonged to stage I and II. This may be due to early impairment of functionality of the patient.

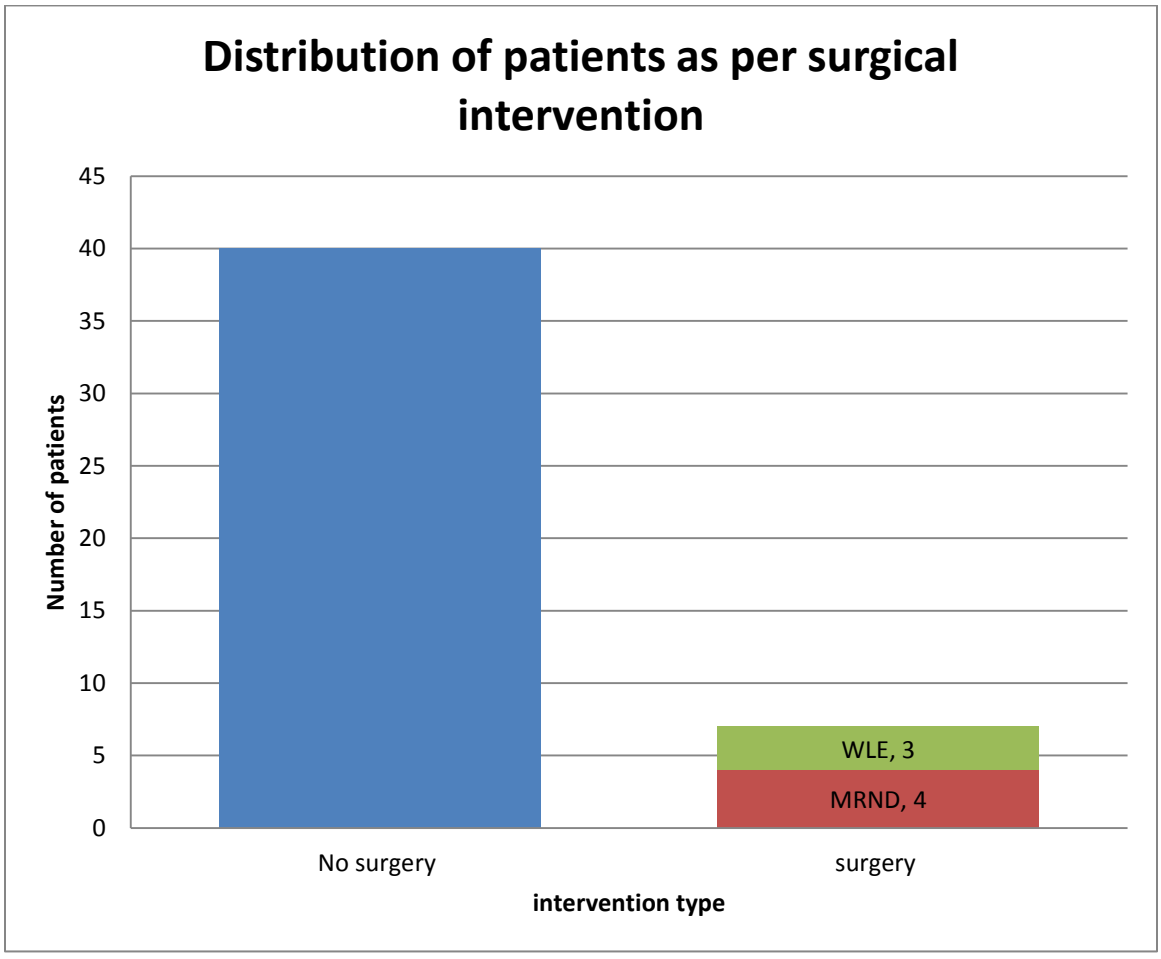
Table –5.7

Distribution of stages according to the disease primary

	I	II	III	IV a	Total
Nasopharynx	0	0	0	2[100%]	2[100%]
Nasal cavity and PNS	0	0	1[100%]	0	1[100%]
Oral cavity	1 [7.69%]	1 [7.69%]	4 [30.77%]	7 [53.85%]	13 [100%]
Oropharynx	0	0	3[50%]	3[50%]	6[100%]
Larynx	4 [22.22%]	8 [44.44%]	4 [22.22%]	2 [11.11%]	18 [100%]
Hypopharynx	1 [14.26%]	1 [14.26%]	0	5 [71.43%]	7 [100%]
Total	6 [12.77%]	10 [21.28%]	12 [25.53%]	19 [40.43%]	47 [100%]

Pre radiotherapy surgical intervention:-

Fig-5.6: Distribution of patients as per the pre radiotherapy surgical intervention.



There were 7 patients, [14.89%] who had undergone surgical intervention for the present disease condition with intent of treatment. Among them 4 [57.14%] had modified radical neck dissection and 3 [42.84%] wide local excision.

The distribution of the surgical intervention as per disease site, and type is as follows-

Table-5.8

Distribution of the surgical intervention as per disease site.

Stage	WLE		MRND	
	Oral cavity	Nasal cavity & PNS	Oral cavity	Nasal cavity & PNS
1	1[50%]	0	0	0
2	0	0	0	0
3	0	0	1[25%]	0
4	1[50%]	1[100%]	3[75%]	0
Total	2[100%]	1[100%]	4[100%]	0

Evaluation status of the patients:-

Table -5.9

Present status of the patients recruited

status	Number (Percentage)
Completed 3rd follow up	6[12.73%]
Completed 2nd follow up	14[42.55%]
Completed 1st follow up	17[78.72%]
Not completed 6 weeks post RT-	3[6.68%]
Loss to follow up(incl. death)	7[14.89%]
total	47 [100%]

Among these patients, there are 3[6.38%] patients who are yet to become evaluable. There have been 7 [14.89%] patients whose follow up data is not available due to either death (1) or loss to follow up. Rest 37[78.72%] patients have come for follow up. Out of those who have come 14 [29.68%] have completed their second and 6[12.77%] have completed their third follow up

Incidence of hypothyroidism:-

Table-5.10

Distribution of patients who have come for follow up according to their thyroid status and time to development

Time of review	Total reviewed	hypothyroid	percentage
6 weeks	37	3	08.10
19 weeks	20	2	10.00
32 weeks	6	0	0.00
Total	37	5	13.51

Till date 5 patients [13.51%] have developed hypothyroidism. Out of them 3 [8.1%] had developed hypothyroidism on the 1st visit i.e., at 6 weeks from the completion of radiation therapy

Fig-5.7: Distribution of patients according to their thyroid status

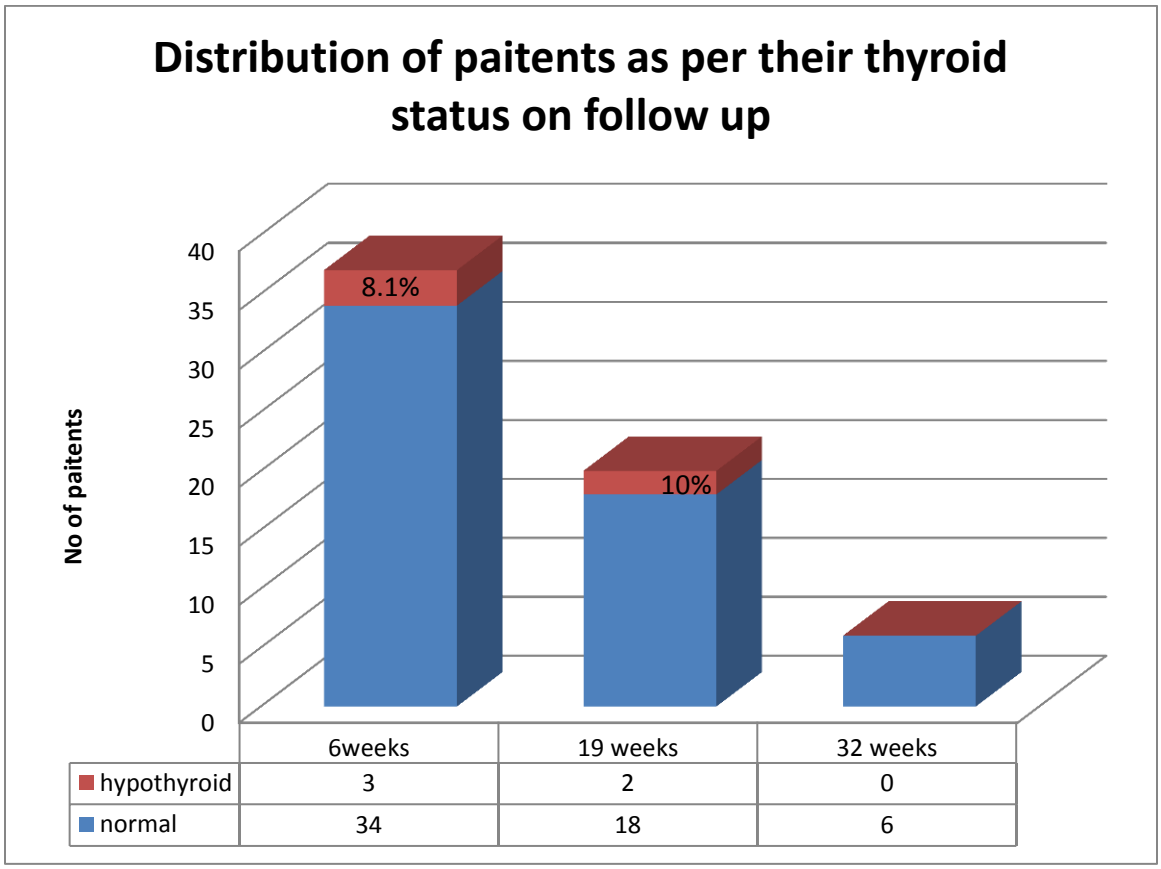
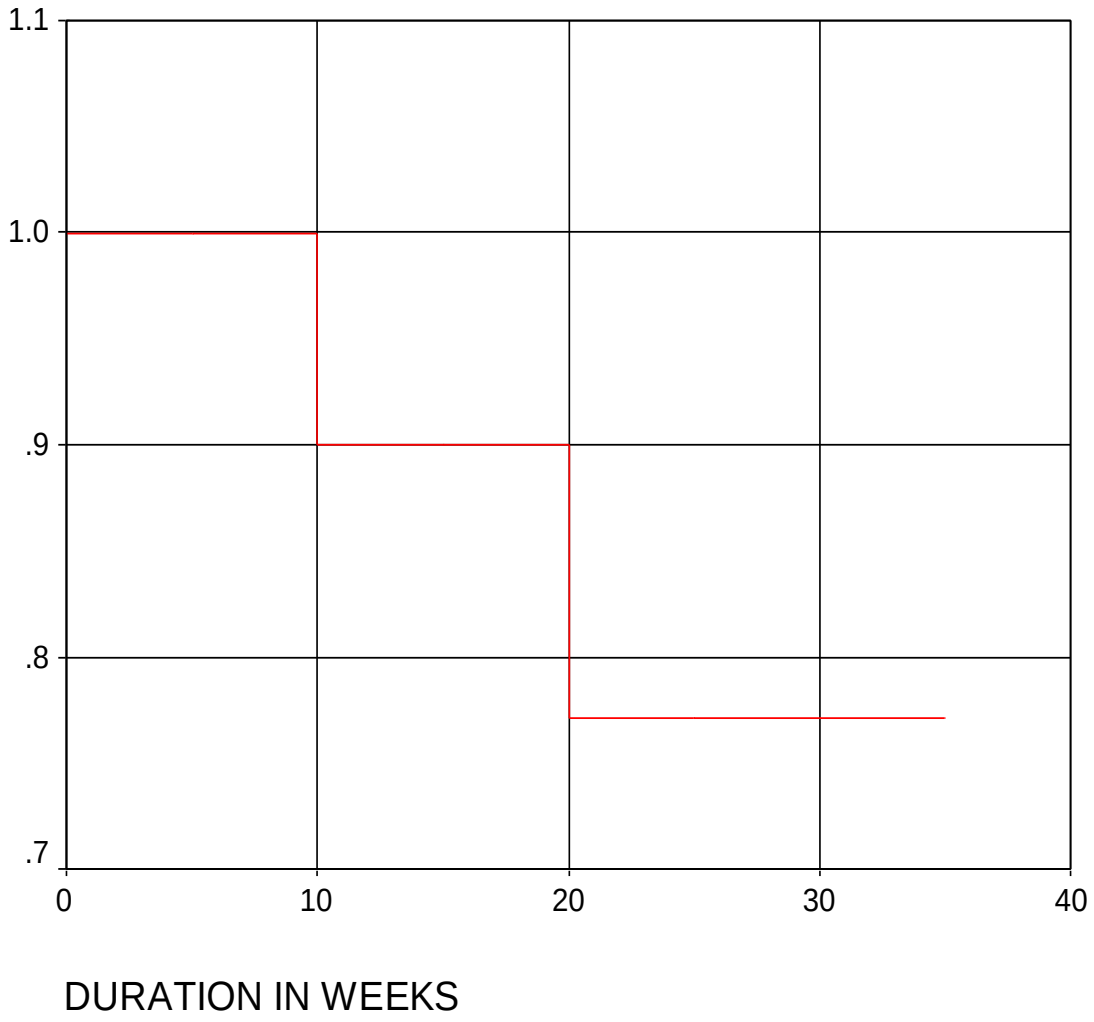


Fig-5.8:

Event free follow up [1-probabilty of developing hypothyroidism] against time



Probability of development of iatrogenic hypothyroidism after radical radiotherapy X axis indicates duration in weeks and Y axis indicates event free probability.

The probability of iatrogenic hypothyroidism as estimated by this is 10% at 10 weeks and 22% at 20 weeks,

The patients were evaluated with TSH, T4 and FTC.

The distribution of the same is shown in the following tables-

Table-5.11

Distribution of TSH of hypothyroid patients at various time frames

TSH	Mean	Std. dev.	minimum	maximum	Range
Baseline	3.1100	.868	1.79	4.20	2.41
1st Fu	6.9380	5.114	.63	12.89	12.26
2nd Fu	24.885	10.98	17.65	32.65	15.53

Table-5.12

Distribution of T4 of new hypothyroid at various time frames

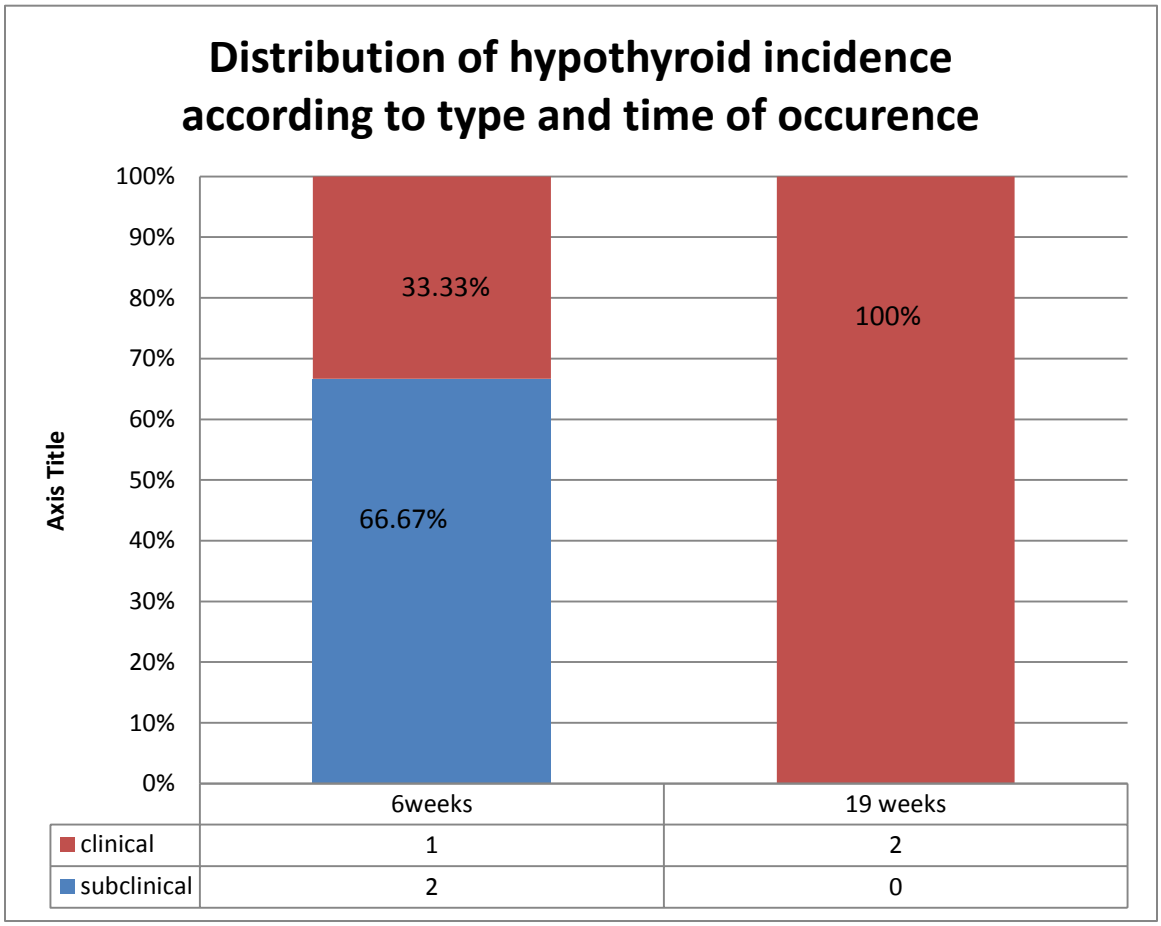
T4	Mean	Std. deviation	minimum	maximum	Range
Baseline	9.24	1.93	7.60	12.30	4.70
1st Fu	7.78	1.08	6.0	8.70	2.70
2nd Fu	6.15	.071	6.10	6.20	0.10

Table-5.13

Distribution of FTC of new onset hypothyroid patients at various time frames

FTC	Mean	Std. dev.	minimum	maximum	Range
Baseline	.9860	.1176	.81	1.10	.29
1st Fu	.9020	.12637	.76	1.10	.34
2nd Fu	.7250	.06364	.68	.77	.09

Fig-5.9:Distribution of hypothyroidism as per type and duration of occurrence.



Out of the 5 patients who had developed hypothyroidism 3 had clinical hypothyroidism and 2 had subclinical hypothyroidism. Both the patients who had developed subclinical hypothyroidism were detected at 6 weeks.

Distribution of patients according to age and occurrence of hypothyroidism was tabulated

Table-5.14

Distribution of patients according to age and hypothyroidism.

Age	Normal	Hypothyroid	Total
<40	2[50%]	2[50%]	4
41-60	22[88%]	3[12%]	25
>60 years	8[100%]	0	8
Total	32	5	37

Out of these 5 patients, who developed hypothyroidism, 2 patients were less than 40 years of age, and 3 were between 41 and 60. None of the patients above 60 years of age developed hypothyroidism in the present cohort.

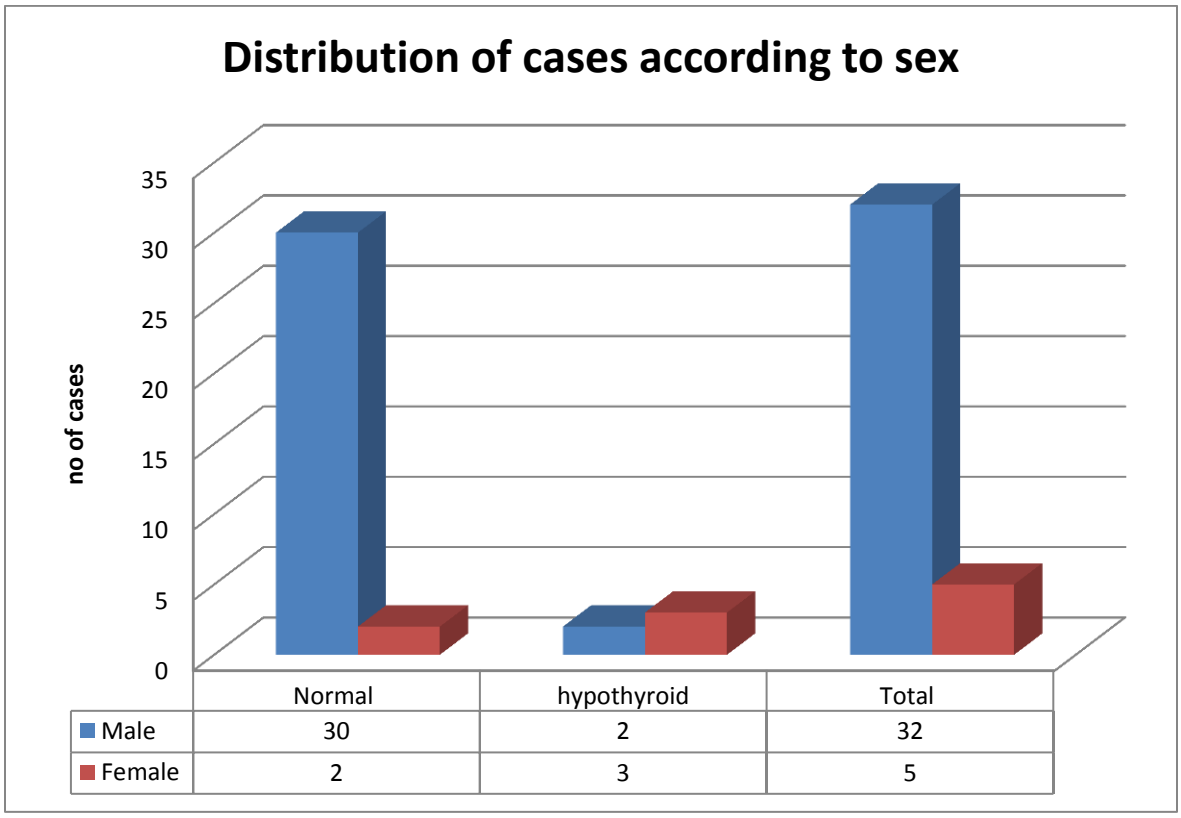
The occurrence of hypothyroidism was more seen in the female subgroup.

Table-5.15: Distribution of hypothyroidism according to sex

	Total	Normal	hypothyroid	P value
Male	32	30[93.75]	2[40%]	.0117
Female	5	2[06.25%]	3[60%]	
Total	37	32	5	

There were 3 female patients who had developed hypothyroidism compared to 2 males, though the number of males was more in the study sample. The test for significance by Fishers exact T test was significant. However, as the absolute number of patients developing hypothyroidism is small the chance of a false positive association cannot be ruled out.

Fig-5.10:Distribution of incidence of hypothyroidism according to sex



Place of residence-

As per the place of residence, only one patient [20%] who had developed hypothyroidism was a resident of Himalayan region.

Table-5.16

Distribution of patients according to occurrence of hypothyroidism and place of residence.

	Hypothyroid	Normal	Total
Himalayan	1[25%]	3[75%]	4
Costal	4[12.12%]	29[87.78%]	33
Total	5	32	37

The incidence did not show any statistical significance. [p=.4555 by 2 tailed Fisher's T test.

Diabetes mellitus-

There were no patients in the hypothyroid group who had DM.

Hypertension:

Out of these 5 patients, 2 were known hypertensive.

Table-5.17

Distribution of patients with occurrence of hypothyroidism and hypertension.

	Hypothyroid	Normal	Total
Hypertension	2[33.33%]	4[66.66%]	6
Normotensive	3[9.68%]	28[90.32%]	31
Total	5	32	37

The incidence did not show any statistical significance. [p=.1771 by 2 tailed Fisher's T test]

Smoking-

As per the habit of smoking there were 3 patients who had developed hypothyroidism.

Table-5.18

Distribution of patients with occurrence of hypothyroidism and smoking.

	Hypothyroid	Normal	Total
Smoker	2[11.11%]	16[88.89%]	18
Non smoker	3[15.79%]	16[84.21%]	19
Total	5	32	37

The incidence did not show any statistical significance. [p=1 by 2 tailed Fisher's T test.

Table-5.19: Distribution of patients according to treatment and development of hypothyroidism

	Total	Normal	hypothyroid	significance
Radical radiotherapy	14	13	1[7.14%]	X2 test value 6.432, df=3, P=.091 Not significant
Radical chemo radiotherapy	19	16	3[15.79%]	
Post-operative radiotherapy	1	0	1[100%]	
Post-operative radio chemotherapy	3	3	0[0%]	
Total	37	32	5	

Table-5.20: Distribution of incidence of hypothyroidism with respect to total dose and fractionation received

Schedule	Total dose	Normal	Hypothyroid	Total
200 cGy x 33 fractions	6600	23	5[17.86%]	28
225 cGy x 28 fractions	6300	4	0	4
Simultaneous boost techniques	Equivalent >66 Gy	5	0	5
Total	-	32	5[13.51%]	37

Table-5.21: distribution of hypothyroidism according to the site and stage of the disease.

	I		II		III		IV a		Total	
	normal	hypo	normal	hypo	normal	hypo	normal	hypo	normal	hypo
Nasopharynx	0	0	0	0	0	0	1		1	0
Oral cavity	1	0	0	0	`1	1	4	1	6	2
Oropharynx	0	0	0	0	1	0	3	0	4	0
Larynx	4	0	5	2	4	0	2	0	15	2
Hypopharynx	1	0	0	0	0	0	5	1	6	1
Total	6	0	5		6		15		32	5

Table-5.22

Distribution of hypothyroidism according to site, stage and treatment modality

A) Oral cavity

Oral cavity	Radiotherapy		chemo radiotherapy		Post op radiotherapy		Post op chemo radiotherapy		total
	Normal	Hypo	Normal	Hypo	Normal	Hypo	Normal	Hypo	
Stage I	0	0	0	0	0	0	1	0	1
Stage III	0	0	0	0	0	1[50%]	1	0	2
Stage IV	1	0	2	1[20%]	0	0	1	0	5
Total	1	0	2	1	0	1	3	0	8

B) Oropharynx:-

Oropharynx	Radiotherapy		chemo radiotherapy		Post op radiotherapy		Post op chemo radiotherapy		total
	Normal	Hypo	Normal	Hypo	Normal	Hypo	Normal	Hypo	
Stage III	0	0	1	0	0	0	0	0	1
Stage IV	0	0	3	0	0	0	0	0	2
Total	0	0	4	0	0	0	0	0	4

C) Larynx:-

larynx	Radiotherapy		chemo radiotherapy		Post op radiotherapy		total
	Normal	Hypo	Normal	Hypo	Normal	Hypo	
Stage I	4	0	0	0	0	0	4
Stage II	5	0	0	2	0	0	7
Stage III	0	0	4	0	0	0	4
Stage IV	0	0	1	0	1	0	2
Total	9	0	5	0	1	0	17

D) Hypopharynx;

Hypopharynx	Radiotherapy		chemo radiotherapy		total
	Normal	Hypo	Normal	Hypo	
Stage I	0	0	1	0	1
Stage IV	2	0	3	1	6
Total	2	0	4	1	7

E) Nasopharynx:-

Nasopharynx	Radiotherapy		chemo radiotherapy		Post op radiotherapy		Post op chemo radiotherapy		total
	Normal	Hypo	Normal	Hypo	Normal	Hypo	Normal	Hypo	
Stage IV	0	0	1	0	0	0	0	0	1
Total	0	0	0	0	0	0	0	0	1

Distribution of the measured dose of radiation received to the thyroid gland region for all evaluable patients was found to be as follows-

Table-5.23:distribution of surface dose to thyroid region for all patients

	Minimum	Maximum	Range	Mean	Std deviation
Dose in cGY	2773.9	6803.81	4029.9	4931.60	1091.53

The distribution of measured dose for the patients who developed hypothyroidism was as follows:-

Table-5.24:distribution of surface dose to thyroid region for all patients

	Minimum	Maximum	Range	Mean	Std deviation
Dose in cGY	4614.05	6369.15	1755.10	5510.48	693.257

All those who had developed hypothyroidism had received more than 45 Gy as measured by TLD to the thyroid region. Out of them 4 had received more than 50 Gy.

However, there were patients in the group, who had received higher doses to the same region, [>50 Gy] but had not developed hypothyroidism till date. The dose measurement was done at the surface level and was based on classical surface anatomy. However, in individual patients, the location of the thyroid gland might have differed significantly, and that the dose received to the thyroid would have varied based on the depth of the thyroid gland, which the surface dose did not take into consideration. Thus, the surface based dosimetry is not an alternative to image based and volume based determination of dose received to thyroid.

Table-5.25 -: Data of patients with iatrogenic hypothyroidism post radiotherapy

ID		1	3	17	26	50
Sex		M	F	F	F	M
Age		60	32	40	55	56
Area		ASSAM	WB	WB	WB	WB
Diagnosis		LARYNX	ORAL CAVITY	ORAL CAVITY	LARYNX	HYPO PAHARYNX
Stage		II	III	IVa	II	III
DM		NIL	NIL	NIL	NIL	NIL
HTN		YES	YES	NO	NO	NO
Habits		SMOKER	NIL	BEETLE NUT	NIL	SMOKER
Treatment		CHEMO-RT	POST OP RT	CHEMO-RT	RT	CHEMO-RT
Dose & fraction		66 Gy 33#	66 Gy 33#	66 Gy 33#	66 Gy 33#	66 Gy 33#
Surface dose to thyroid region		5946.444	6369.154	5548.191	5074.554	4614.053
Baseline [pre RT]	TSH	1.79	3.02	3.38	3.16	4.20
	T4	8.60	12.30	9.90	7.60	7.80
	FTC	1.10	1.02	0.93	0.81	1.07
	FACT-T	114	86	96	97	92
1st follow up	TSH	0.63	9.75	8.75	2.67	12.89
	T4	8.60	7.70	7.90	8.70	6.00
	FTC	1.10	0.76	0.85	0.93	0.87
	FACT-T	108	99.00	96	102.00	93
2nd follow up	TSH	17.12			32.65	
	T4	6.10			6.20	
	FTC	0.68			0.77	
	FACT-T	99			98	

Signs of hypothyroidism:

The followings signs were asked for from the patients in form of thyroid questionnaire.

The responses were divided into those obtained from patients at hypothyroid state and those in euthyroid state. There were a total of 58 post radiotherapy evaluable responses, at the time of detection of hypothyroidism.

In first follow up,

symptoms		Total (n)	Euthyroid	Hypothyroid	p-value
Fatigue	Present	3	3	0	1
	Absent	34	31	3	
	Total	37	34	5	
Weight gain	Present	8	5	3	.0072
	Absent	29	29	0	
	Total	37	34	3	
Constipation	Present	3	1	1	.1577
	Absent	34	33	2	
	Total	37	34	3	
Dry skin	Present	1	0	1	.081
	Absent	36	34	2	
	Total	37	34	3	
Cold intolerance	Present	2	0	2	.0045
	Absent	35	34	1	
	Total	37	34	3	

Appetite	Present	8	7	1	.14
	Absent	29	27	2	
	Total	37	34	3	

Fatigue, weight gain, dry skin, and cold intolerance were found to be significantly associated with incidence of hypothyroidism. Only one patient in the euthyroid group elicited a positive response of temper fluctuation, [patient had same response at base line] and one complained of joint pain. The last patient was known to be suffering from OA for the past 12 years and was on treatment. These tend continued in the cumulative data from the first and second follow up.

symptoms		Total (n)	Euthyroid	Hypothyroid	p-value
Fatigue	Present	9	5	1	.4390
	Absent	48	47	4	
	Total	57	52	5	
Weight gain	Present	9	6	3	.0241
	Absent	48	46	2	
	Total	57	52	5	
Constipation	Present	3	1	2	.018
	Absent	54	51	3	
	Total	57	52	5	
Dry skin	Present	3	0	2	.0063
	Absent	54	52	3	
	Total	57	52	5	
Cold	Present	3	0	3	.0003

intolerance	Absent	54	52	2	
	Total	57	52	5	
Appetite	Present	11	8	2	.2077
	Absent	46	44	3	
	Total	57	52	5	

Fatigue, loss of appetite was present across the groups in both follow ups and was not significantly associated with the development of hypothyroidism in the post radiotherapy head and neck patients.

QUALITY OF LIFE ANALYSIS

The quality of life was estimated by FACT score. The data so collected was analyzed and found that the total FACT scores had a significant improvement from the base line when tested with Wilkinson signed rank test.

But the FACT score for those with hypothyroidism did not show any difference from baseline value, when compared to that at the point of developing of hypothyroidism. [p=.068]

This suggests that the improvement in quality of life, post radiotherapy, was not significant when the patient develops hypothyroidism.

	Comparing values	**Test used**	**Null hypothesis**	**P value**	**Result**
1. All patients	Total [baseline Vs. first follow up]	Wilcoxin signed rank Test	Median of differences between two groups are not significant	.000	Reject null hypothesis
2. All patients	Total [baseline and last available]	Wilcoxin signed rank Test	Median of differences between two groups are not significant	0.000	Reject null hypothesis
3. New onset hypothyroid patients	Total [baseline and at time of detection of hypothyroidism]	Wilcoxin signed rank Test	Median of differences between two groups are not significant	0.68	Retain null hypothesis

Discussion

Discussion

Hypothyroidism is found to be one of the long term side effects in patient undergoing radiotherapy for head and malignancies. It affects the quality of life but can be treated with thyroxine supplementation once detected. Treatment with thyroxine supplementation prevents complications of hypothyroidism.

In the present study, the incidence of baseline hypothyroidism among the screened individuals was about 11%. This is similar to that reported by Shantha et al i.e. 8.8%.(29)

During the study, 5 patients [13.51%] developed hypothyroidism during follow up. Out of these five patients who had developed hypothyroidism, 2 were below 40 years of age, and 3 were between 41-60 years of age. There were no patients above 60 years of age. However, this was not of any statistical significance. A similar trend is seen in the findings on the Indian population by Aich et al in which the development of hypothyroidism was not related to age. (3)

.

Out of the 5 who had developed hypothyroidism 3 were female and 2 were male. The difference was statistically significant [p=.0117]. Alkan et al in his study also found female predominance but in an Indian study by Aich et al there was not association with sex.(30)

Among the patients who had developed hypothyroidism, 3[60%] had received concurrent chemotherapy with Cisplatin [40 mg/m2] and the remaining 2 had only radical radiotherapy. This finding was not statistically significant. [P value of 1 by two tailed Fischer's test]. In a study done by Aich et al there was no association between occurrence of hypothyroidism and concurrent chemotherapy with radiotherapy. (3)

In our study there was no significant relation of occurrence of hypothyroidism to the site of the disease, or stage of the disease. There was also no significant difference with respect to surgery, associated DM and hypertension.

There seems to be a correlation between baseline TSH and development of hypothyroidism with 4 of the 5 patients (75%) who developed hypothyroidism on follow up post radiotherapy had a baseline TSH level more than 3. On the other hand among the remaining 32 patients who had normal thyroid function during follow up only 2 had baseline TSH levels more than 3.

The measured surface dose to the thyroid region was not significantly associated with, the incidence of hypothyroidism. This is probably because the thyroid gland itself may vary in position and depth from patient to patient and therefore the surface dose based on surface marking of the thyroid may not be representative of the dose received to the thyroid gland. Alterio et al has also reported that point dose does not correlate with the incidence of hypothyroidism. (33)

Among the 5 patients who developed hypothyroidism following radiotherapy in our study 3 [8.1%] occurred at first follow up [6 weeks post completion of radiotherapy] and 2 at second follow up [19 weeks post completion of radiotherapy]. This is much higher and earlier than that documented by Aich et al which were 0.57% at 6 weeks and 3.6% at 6 months. Ref However there is data from far eastern population reported by Nishiyama et al which was similar to ours with significant rise in TSH at 4.5 months following completion of radiotherapy. (45)

Though the incidence did not vary significantly from that of the western population as reported by Alkan et al what varied is the early onset of hypothyroidism in present group. ,(3)

Most of the western literature had stressed on the development of hypothyroidism as a late complication of the treatment and therefore recommended evaluation at a later stage after completion of treatment. This study shows that the Indian population is different from the western population in terms of early onset of hypothyroidism. The reason of such early onset may be due to genetic or environmental factors and needs to be explored.

The clinical symptoms generally associated with hypothyroidism [like fatigue, constipation, loss of appetite] are commonly present in most head and neck patients especially at the end of radiotherapy . In this study one of the hypothyroid patients complained of fatigue and 3 out of 5 patients were found to have weight gain. The occurrence of cold intolerance, [P=0.0045] in the first follow up and weight gain among the patients who developed hypothyroidism compared to the remaining euthyroid patients was found to be statistically significant[P=0.0072]. These symptoms were elicited only on asking as patients never took weight gain or cold intolerance as significant symptoms to be reported. Other symptoms like temper fluctuation, joint pain was not found in the present cohort. Occurrence of constipation, loss of appetite among those who developed hypothyroidism and the euthyroid patients, was not found to be statistically significant.

The cumulative data at second follow up continued to show similar findings except for constipation and dry skin which now was of statistical significance.

Evaluation of the quality of life score showed improvement in the median scores of patients who did not develop hypothyroidism following radiotherapy. There was neither improvement nor worsening in the patients who developed hypothyroidism, denoting a relatively poorer quality of life in these patients.

Limitations of the study:-

The present analysis of the study is limited by the fact that all patients who have been recruited have still not reached the 6 weeks follow up period and are therefore not evaluable.

Longer follow up data is required to make significant observations about incidence and the impact of hypothyroidism in Indian population in comparison with those reported in literature.

Inclusion of less number of patients undergoing conformal radiotherapy and less number of post op patients in the study.

Conclusion

Conclusion -

Based on the present data it can be concluded that

1. Hypothyroidism at baseline evaluation was 11% and the incidence of secondary hypothyroidism post radiotherapy was 13.51% --
2. Surface dose measurements as described in the earlier literature did not correlate with clinical outcome and should be looked into in the light of 3D organ imaging and dose volume relationships in the era of modern radiotherapy.
3. The significant clinical symptoms of secondary hypothyroidism are cold intolerance and weight gain seen as early as six weeks.
4. Iatrogenic hypothyroidism occurred over a variable point of time during the follow up period as early as 6 weeks and at 19 weeks of completion of radiotherapy.
5. Females appeared to be more prone to develop post radiotherapy hypothyroidism.
6. Those patients with TSH levels more than 3 m IU/ml at base line were found to be more prone to develop secondary hypothyroidism.
7. Hypothyrodism is a significant comorbid association at presentation which can worsen with radiotherapy and early institution of treatment results in improvement of quality of life. In view of this, a baseline and follow up TSH as routine should be incorporated in the management

schedule. This simple biochemical screening is a cost effective strategy to improve the quality of life in head and neck cancer.

Recommendations

Recommendations:-

1. Follow up of the present study to the planned duration of follow up
2. Further study based on volumetric data for determination of dose volume relationship with incidence of hypothyroidism.

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Annexure

Annexure

CHRISTIAN MEDICAL COLLEGE
VELLORE - 632 002, INDIA.
INSTITUTIONAL REVIEW BOARD (IRB)

Dr. George Thomas, D.Orth
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Deputy Chairman, IRB &
Additional Vice Principal (Research)

November 16, 2009

Dr. Suparna Kanti Pal
PG Registrar
Department of Radiotherapy
Christian Medical College
Vellore 632 004

Sub: FLUID Research grant project NEW PROPOSAL:
A prospective study to determine the occurrence of hypothyroidism following treatment with radiation therapy in patients of head and neck carcinomas and the influencing factors.
Dr. Suparna Kanti Pal, PG Registrar, Radiotherapy, Dr. Subhashini John, Dr. Rajesh B, Dr. Rajesh I, Dr. Patricia S, Dr. Saikat Das, Radiation Therapy.

Ref: IRB Min. No. 7003 dated 11.11.2009

Dear Dr. Pal,

The Institutional Review Board (Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "A prospective study to determine the occurrence of hypothyroidism following treatment with radiation therapy in patients of head and neck carcinomas and the influencing factors" on November 11, 2009.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Patient Information Sheet and Informed consent Form (English, Tamil, Hindi and Bengali
3. Cvs of Drs. Suparna Kanti Pal, Subhashini John, Rajesh Balakrishnan, Rajesh Isiah Gunasingam, Patrica Solomon and Saikat Das.
4. A CD containing document 1-3

The following Ethics Committee members were present at the meeting held on November 11, 2009 at 10:00 am in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
Dr. George Thomas	MBBS, D.Ortho	Chairperson (IRB) & Orthopaedic Surgeon, St. Isabel Hospital, Chennai &	Non-CMC Staff.

CHRISTIAN MEDICAL COLLEGE
VELLORE - 632 002, INDIA.
INSTITUTIONAL REVIEW BOARD (IRB)

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Chairman, Ethics Committee

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Deputy Chairman, Ethics Committee

Dr. L. Jeyaseelan, MSc,PhD
Secretary, IRB

Dr. George Mathew, MS,MD,FCAMS
Chairman, Research Committee &
Principal

Dr. Gagandeep Kang, MD,PhD,FRCPath
Deputy Chairman, IRB &
Additional Vice Principal (Research)

		Editor, Indian Journal of Medical Ethics	
Dr. Shuba Kumar	MA, MSc, Ph.D.	Dy. Chairperson (IRB) & Social Scientist, SAMRATH, Chennai.	Non-CMC Staff.
Dr. George Mathew	MBBS, MS, MD	Principal, C.M.C.	
Dr. Thambu David (on behalf of Dr. Lionel Gnanaraj)	MBBS, MS, M.Ch. (Urol)	Medical Superintendent, CMC.	
Dr. Prathap Tharyan	MD, MRCPsych.	Associate Director, Professor of Psychiatry, CMC	
Rev. Malhia Joshua (on behalf of Rev. Dr. T. Arul Dhas)	M.Sc., BD, Ph.D.	Chaplain, CMC	
Mr. Harikrishnan	BL.	Lawyer	Non-CMC staff.
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M.Phil, BL.	Legal Advisor, CMC.	
Dr. Denny Fleming	MBBS, MD	Professor, Pharmacology Dept. CMC.	
Dr. Sujith Chandy	MBBS, MD	Professor, Pharmacology Dept. CMC.	
Mrs. Radha Anil	M.Sc.	Correspondent, Apple Kids, Sathuvachari, Vellore.	Non-CMC staff.
Rev. Dr.S.G.Immanuel	PhD, MDIV	Pastor, Vellore	Non-CMC-Staff
Dr. Srinivas Babu	MSc, Ph.D.	Sr. Scientist, Neurological Sciences, CMC.	
Mrs. S. Pattabhiraman	BSc, DSSA	Social Worker, Vellore	Non-CMC-Staff
Dr. Suresh Devasahayam	BE, MS, PhD	Professor of Bioengineering, CMC	
Dr. Gagandeep Kang	MD, PhD, FRCPath.	Dy. Chairperson (IRB), Professor of Microbiology & Addl. Vice Principal (Research), CMC.	

We approve the project to be conducted in its presented form.

The Institutional Ethics Committee / Independent Ethics Committee expects to be informed about the progress of the project, any SAE occurring in the course of the project, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

A sum of Rs. 30,000/- (Rupees Thirty thousand only) is sanctioned for 1 year out of which a maximum of Rs. 1,500/- can be spent for stationery, printing, Xeroxing and computer charges (if computers used are within the institution).

Yours sincerely,

L. Jeyaseelan

Dr. L. Jeyaseelan Ph.D.
Secretary, Institutional Review Board

Secretary
Institutional Review Board
(Ethics Committee)
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Vellore - 632 002, Tamil Nadu, India.

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Clinical Trials Registry - India (CTRI)

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UTRN.WHO	**TEMP UTRN 063315413-0212200915042508**
Reference No and Date	**REFCTRI-2009 001007, 02-12-2009**
Submitted By and Date	SUPARNA KANTI PAL, 10-12-2009
CTRI No.and Date	**CTRI/2009/091/001007, 10-12-2009**
Status of TrialWHO	**Open to recruitment**

IDENTIFIERS		
UTRN.WHO*	**TEMP UTRN 063315413-0212200915042508**	
Public Title StudyWHO*	A prospective study to determine the occurrence of hypothyroidism following treatment with radiation therapy in patients of head and neck carcinomas and the influencing factors	
Scientific Title of StudyWHO*	A prospective study to determine the occurrence of hypothyroidism following treatment with radiation therapy in patients of head and neck carcinomas and the influencing factors	
Secondary IDsWHO	**Secondary ID**	**Registry**
	REFCTRI-2009 001007	CTRI

CONTACT INFORMATION OF INVESTIGATORS & SPONSORS			
Principal Investigator or overall Trial Coordinator (multi-center study) Details.			
Principal Investigator's Name	Dr Suparna Kanti Pal	Email ID	suparna@cmcvellore.ac.in
Address line 1	Departemnt of RT II, Christian Medical College Hospital	Address line2	IDA scudder Rd
City	Vellore	State	TN
Postal Code	632004	Country	India
Contact No.	04162282046	Fax No.	(0416)2232035/2232103
Contact Person (Scientific Query).WHO			
Name of the contact person(Scientific query)	Dr. Subhashini John	Email ID	subha@cmcvellore.ac.in
Address line 1	Department of RT,	Address line2	IDA scudder Rd

	CMC Hospital		
City	Vellore	State	TN
Postal Code	632004	Country	India
Contact No	04162282046	Fax No.	(0416)2232035/2232103
Affiliation			
Contact Person (Public Query).WHO			
Name of the contact person(Public query)	Dr. Subhashini John	Email ID	subha@cmcvellore.ac.in
Address line 1	Department of RT, CMC Hospital	Address line2	IDA scudder Rd
City	Vellore	State	TN
Postal Code	632004	Country	India
Contact No.	04162282046	Fax No.	(0416)2232035/2232103
Source/s of Monetary or Material SupportWHO	**Source/(S) Of Monetary Or Material Support**: INSTITUTIONAL FUNDING From Fluid Reserch Grant Fund Christian Medical College, Vellore		
Primary SponsorWHO	Dr. Suparna Kanti Pal		
Secondary SponsorWHO	**Secondary Sponsor**: NIL		
Countries of RecruitmentWHO	**Countries Of Recruitment**: India		
Details Site/s of study (details of responsible contact person at each site)			
Number of Sites	1		
Site/s Details	**Site Address**: Department OF RT Unit -II; **Contact Person**: Dr. Subhashini John		
REGULATORY APPROVALS			
Ethics Committee*	**Ethics Committee Name**: Institutional Review Board(Ethics Committee) CMC, Vellore; **Approval Status**: Approved		
Regulatory Approval obtained from DCGI*	Not Applicable		

METHODS

Health Condition/Problems Studied[WHO]	Incidence of clinical and subclinical hypothyroidism in patients undergoing radiation for head and neck carcinomas
Study Type[WHO]	Other
Intervention and Comparator/Control agent[WHO]	
Intervention Name	**Intervention** / **Other Details(Dose, Duration, Etc)**: NIL / NIL
Control Intervention Name	**Control Intervention** / **Other Details(Dose, Duration, Etc)**: NIL / Not Applicable
Key Inclusion/ Exclusion Criteria[WHO]	Inclusion Criteria: 1.Adult patients with non metastatic Head & Neck carcinoma of the following sites- I.Hypopharynx II.Larynx III.Oropharynx IV.Oral cavity V.Nasal cavity without intracranial extension VI.Nasopharynx without intracranial extension VII.Carcinoma of unknown primary 2.Patients receiving radiotherapy(>50 Gy) as part of treatment 3.Radiation field extending to lower neck , unilateral or bilateral 4.Performance score- ECOG-0 to 2 Exclusion Criteria: 1.known to have hypothyroidism at the time of screening or the history of the same in the past, for which he/she is currently on supplements 2.who has a history of previous exposure to radiation therapy in Head and neck region 3.Carcinomas with intracranial extension
Method of generating randomization sequence	Not Applicable
Method of allocation concealment	Not Applicable
Blinding and masking	Not Applicable
Primary Outcome[WHO]	
Outcome name	**Primary Outcome** / **Timepoints**: Hypothyroidism / At 6 Weeks, 18 Weeks And 30 Weeks Following Competion Of Radiotherapy
Key secondary outcome/s[WHO]	
Outcome name	**Secondary Outcome** / **Timepoints**: Factors Influencing The Occurrence Of Hypothyroidism / 6 Weeks, 18 Weeks And 30 Weeks Following Completion Of Radiation Therapy

Target sample size[WHO]		Phase of Trial*	Not Applicable
Date of first Enrollment[WHO]	16- 12- 2009 [date-month-year]	Estimated duration of trial	Years
Status of Trial[WHO]*	Open to recruitment		
Brief Summary	The cohort study would include study population who are undergoing radiotherapy to the neck region for head and neck carcinomas. We would determine clinical and biochemical status with respect to thyroid function, before starting of radiotherapy (as a screening test), at 1st follow up and up to 3rd follow up (from 6 weeks to about 7.5 months[30 weeks] of completion of radiation treatment). The 1st of these i.e., the one before starting radiotherapy would also act as screening test for inclusion into the study. The patients would be classified as per demographic parameters (age, sex, place of domicile), sub site of the disease, dose to thyroid (maximum dose, dose with respect to thyroid volume), treatment co- factors, (concurrent chemotherapy and surgery with unilateral and bilateral MRND) and other factors if any. During radiotherapy for patients who have a planning CT or a diagnostic CT scan, the DVH generated would be used to determine the volume of the thyroid irradiated and the dose. For all patients (both conventional and conformal) point dose measurement of the thyroid gland would be done during treatment using a diode or TLD. Anybody found to have hypothyroidism at the time of screening would not be included for further evaluation. If a patient who after inclusion in the study develops subclinical or clinical hypothyroidism would be referred to endocrinology for the management of the same. Such patients are considered to have reached end point. Once the study is complete, the available data would then be analysed and tabulated with respect to occurrence of hypothyroidism and the results would then be analysed for significance of the factors.		

Information sheet for participants

A prospective study to determine the occurrence of hypothyroidism following treatment with radiation therapy in patients of head and neck carcinomas and the influencing factors

Name- _____

You are hereby being requested to participate in the above mentioned study.

1. **What is the study all about**-

   Patients receiving radiation for head and neck malignancy are found to develop hypothyroidism i.e.; low thyroid hormones. The actual incidence, in Indian population is difficult to predict as there has been varying rates predicted in various studies n the west. While there have been some Indian studies looking into the same for conventional treatment there is not much published data regarding, 3DCRT and IMRT. We are trying to get an appropriate data for all types of radiation.

2. **What will be done?** –

   You will have to undergo, a small blood test (TSH/ TFT) before the treatment begins and 6 weeks (1^{st} FU), 18 weeks(2^{nd} FU) and 30 weeks (3rd FU) after the completion of treatment. Such blood tests are regular protocol in some western countries. We will also measure the radiation dose to the thyroid gland by means of TLD while on treatment. It will NOT result in any additional dosage of radiation nor will it alter the treatment pattern form that what you would have received if

you were not a part of the study. You will have to answer a questionnaire on your thyroid function which will take hardly 5-10 min. We will after getting all the results compare between various groups and subgroups.

3. **Description of any reasonably foreseeable risks or discomforts to the Subject-**

In addition to the regular treatment related procedures, you will be asked to undergo small blood tests, as mentioned. Apart from the small pricking sensation while collecting blood we do not fore see any other risks or discomfort

4 Is **there any benefit in getting enrolled in the study?**

There is no change in treatment plan. You would undergo clinical and biochemical diagnostic test for hypothyroidism, so if you are found to have thyroid disorder at any point of time, it would be diagnosed early and would be sent for necessary management. As quite a good number of patients do develop hypothyroidism in post RT period, it might help you to improve the quality of life

5. **Disclosure of specific appropriate alternative procedures or therapies available to the Subject.**

There will be no change of treatment from the standard procedures, which are same as if you have even been not a participant in the trial. Head neck malignancies are treated with either single modality or multi modality depending on the stage of the disease. You will be treated as per your staging as per your decision to undergo the same.

6. **What about the data security**-

The data so collected will only be used for research purpose and not any other purpose and will not be supplied to any person or body except those authorised (investigators, institutional review board, ethics committee, professional bodies or any legal authorities whenever required). However, in any matter, your identity will be protected and will not be revealed.

7. **Trial treatment schedule(s) and the probability for random assignment to each treatment (for randomized trials**)

The treatment, schedule will include about 6 ½ weeks of radiotherapy , 5 days a weeks, once daily, with or without chemotherapy as per your requirements and as per the method of radiotherapy you choose (IMRT/ Conventional 2 D/ 3 DCRT). Interruption of treatment consequent to radiations reactions or any co-morbidities or any other general illness during the period would be decided at par with any other non- trail patients, Break of radiotherapy consequent to machine breakdown or other causes would be as in case of any other non-trial patients.

There is no provision of any randomisation.

8. **Compensation and/or treatment(s) available to the Subject in the event of a trial-related injury**

We are not adding or removing any component of your treatment, therefore the possibility of treatment for trial related injury does not arise.

9. **An explanation about whom to contact for trial related queries, rights of Subjects and in the event of any injury**

For any trail related quarries the principal investigator or any co- investigators can be contacted at-

Dr. Suparna Kanti Pal, department of radiotherapy

Dr Subhashini John Department of Radiotherapy

Dr. Rajesh B, Department of radiotherapy

Dr. Rajesh I, Department of radiotherapy

Dr. Patricia S, department of radiation therapy

Dr. Saikat Das, Department of Radiation Therapy

10. **Monetary considerations**-

No money or compensation in any form will be given for participating in this study

11. **Subject's responsibilities on participation in the trial**-

The subject's responsibility in this trial is limited to undergo the treatment as per medical advice and undergo tests as required and answer the questionnaire at

scheduled time. The patient is also expected not to delay inordinately in his/her follow up. If the patient refuses to answer the questionnaire or refuses to answer the questionnaire , after clearing any doubts about the tests or questionnaire or regarding the study , he /she will deemed to have expressed his or her desire to be excluded form the study and will be regarded as been withdrawn from the study

12.

Participation-

The participation is purely voluntarily. No monetary compensation or otherwise will be provided

Can I leave the study-?

Surely, any moment you want to. Such a decision will no way change the treatment or follow up in future

1.2 Additional elements, which may be required

a. **Foreseeable circumstances under which the Subject's participation may be terminated by the Investigator without the Subject's consent**.

If you are found to have any thyroid disorder at any stage of evaluating you would be sent to the Endocrinology OPD for the relevant treatment, if required. In case this is before the initiation of treatment you would be considered as screening failure and will not be a part of the study. In event of such development after the treatment you will be considered having reached the

primary endpoint . However in any of these situations, you will continue to have appropriate standardised care at par with all other trial and non-trial patients.

b**. Additional costs to the Subject that may result from participation in the study**:

As a participant of the study you will be asked to undergo some blood tests and answer some questions. This blood tests are routine in nature and will cost you about INR 770/-.

There will be no additional cost of treatment.

c. **The consequences of a Subject's decision to withdraw from the research and procedures for orderly termination of participation by Subject**.

As mentioned earlier, you can withdraw, from the study any moment you wish to. You would not be asked to furnish any reason neither your treatment nor follow up would get affected. However, we would like to hear from you the reasons if you please, and clear any doubts that may have risen.

d. **Can I know about my results**-?

Surely, you will be provided with the results. If you are found to be having or suspected of thyroids dysfunction you will be immediately informed and be referred to Endocrinology OPD who deal with such problems. Under no circumstances any information of your problem will be concealed from you.

e. Any treatment with radiotherapy or chemotherapy involves risks to fetus or embryo, and therefore we would ask you to confirm that you are not pregnant at time of the treatment and take appropriate contraceptive measures to prevent

pregnancy during the treatment and till at least for the next follow up, if you were on chemotherapy.

Nursing mothers are advised not to wet nurse the baby till all chemotherapy is over and till 1st follow up.

This is applicable to all patients undergoing radiotherapy or chemotherapy irrespective of the fact that you are a part of the trial or not. Even if you wish to withdraw from the trial, these precautions are to be taken.

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:

_____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness: _____

Date: _____/_____/_____

Name of the Witness: _____

Informed consent form

Study Title: A prospective study to determine the occurrence of hypothyroidism following treatment with radiation therapy in patients of head and neck carcinomas and factors influencing this

Study Number:

Subject's Initials: _____ Subject's Name: _____
Date of Birth____/____/_____(DD/MM/YYYY) / Age: _____yrs
Please initial box
(Subject)
(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]
(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]
(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]
(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]
(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____
Date: _____/_____/_____
Signatory's Name: _____

Signature of the Investigator: _____
Date: _____/_____/_____
Study Investigator's Name: _____

Signature of the Witness: _____
Date:_____/_____/_____
Name of the Witness: _____

Thyroid questionnaire-1*

Name-

Hospital no-

Study no-

Date of assessment-

Visit- initial /end of RT / 1st FU / 2ND U /3RD FU

Body weight-

Neck swelings-

1. **Are u fatigued?**- Not at all/always had-moderate symptoms-severe symptoms
2. **are u gaining weight?**- Not at all/always had-moderate symptoms-severe symptoms
3. **do you have constipation?**- Not at all/always had-moderate symptoms-severe symptoms
4. **do you have dry skin?** Not at all/always had-moderate symptoms-severe symptoms
5. **do you feel cold even when others do not?**- Not at all/always had-moderate symptoms-severe symptoms

* standard validated questionnaire (ref-Galbo et al 2009; the prevalence of hypothyroidism after treatment for laryngeal and hypopharyngeal carcinomas: are auto antibodies of influence? :Acta oto Laryngologica,127:3,312-317

Thyroid questionnaire-2*

Name-

Hospital no- _____ Study no-

Date of assessment-___/____/20___ Visit- initial /end of RT / 1st FU / 2ND FU /3RD FU

Body weight-_____kg

Neck swellings-

1. **Are u fatigued even after adequate rest and sleep?**- Not at all/always had-moderate symptoms-severe symptoms
2. **are u gaining weight?**- Not at all/always had-moderate symptoms-severe symptoms
3. **do you have constipation?**- Not at all/always had-moderate symptoms-severe symptoms
4. **do you have dry skin?** Not at all/always had-moderate symptoms-severe symptoms
5. **do you feel cold even when others do not?**- Not at all/always had-moderate symptoms-severe symptoms
6. **Do you loose your temper often?** - Not at all/always had-moderate symptoms-severe symptoms
7. **Have your appetite decreased?** - Not at all/always had-moderate symptoms-severe symptoms
8. **Is there any joint pain or numbness of the limbs** - Not at all/always had-moderate symptoms-severe symptoms

* questionnaire generated by CMC

FACT-H&N (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-H&N (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-H&N (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
H&N1	I am able to eat the foods that I like	0	1	2	3	4
H&N2	My mouth is dry	0	1	2	3	4
H&N3	I have trouble breathing	0	1	2	3	4
H&N4	My voice has its usual quality and strength	0	1	2	3	4
H&N5	I am able to eat as much food as I want	0	1	2	3	4
H&N6	I am unhappy with how my face and neck look	0	1	2	3	4
H&N7	I can swallow naturally and easily	0	1	2	3	4
H&N8	I smoke cigarettes or other tobacco products	0	1	2	3	4
H&N9	I drink alcohol (e.g. beer, wine, etc.)	0	1	2	3	4
H&N 10	I am able to communicate with others	0	1	2	3	4
H&N 11	I can eat solid foods	0	1	2	3	4
H&N 12	I have pain in my mouth, throat or neck	0	1	2	3	4

Serial no-_____

Date- / /____

A prospective study to determine the occurrence of hypothyroidism following treatment with radiation therapy in patients of head and neck carcinomas and factors influencing this

Patient serial no in study-_____

Name-

Hospital no-_____RT NO- ____/____/RT II

Address-_____

_____

State-_____ PIN-_____

Home Ph-_____ Mobile-_____

Local Ph No_____

DOB/Age (in yrs)-_____/____/_____ (_____)

Sex- M/F

Diagnosis-_____

Staging (TNM, stage format) - T___N____M____ stage _____

Any prior cancer directed treatment-Yes/No

Any prior history of other malignancy- Yes/No

Any prior history of radiation therapy for benign or malignant disorders- Yes/No

Any history of thyroid disorders- Yes/No

Any co-morbid conditions-

DM- /HTN- /BA-

Others

Audio logical status-

Eligibility check list:-

1. **Age- adult- Yes/No**
2. **Site-**
    a. **Hypo pharynx**
    b. **Larynx**
    c. **Oral cavity**
    d. **Nasal cavity without ICE**
    e. **NPX without ICE**
    f. **CUP**
    g. **None**
3. **P.S.- 0/1/2/None**
4. **Radiation field extends to neck- Yes/No**
5. **Intention to treat- >50 Gy Yes/ No**
6. **History of RT to neck- Yes/ No**
7. **currently on thyroid supplements-Yes/NO**
8. **Intracranial extension present-Yes/No**

Eligible for screening- Yes/No

Pre treatment

TSH-

T4

FTC

Subject status- Included/ Excluded/ Screening failure

Treatment details-

Radiotherapy-

Type-

Dose-

Dose to thyroid (point)

Volume of thyroid irradiated-(as calculated from TPS)

Pre-RT surgery- Yes/ No

If yes type-

MRND- Yes-(unilateral/ Bilateral)/ No

Neo- adjuvant chemotherapy- yes/no

No of cycles-

Drug and dose used-

Concurrent chemotherapy-Yes/No

Drug and dose used

No of cycles-

Adverse events during RT (if any)-

	Date	ECOG	Diet status (CTC V3)	Skin reactions (CTC V3)	Oral cavity(CTC V3)	Body wt (kg)	SEP© cm	SEP(N) cm	Comments Seen by	Others if any events
Beginning										
Week-1										
Week-2										
Week-3										
Week-4										
Week-5										
Week-6										
Week-7										
End of RT										

	ECOG	Disease status	Audio status	Quality Of Life	Clinical assessment	TSH level	T4 level	FTC level
Screening(day 0)								
End of RT assessment								
1st follow up (6 weeks)								
2nd follow up (18 weeks)								
3rd follow up (30 weeks)								

Demographic and treatment details of the evaluable patients

ID	SEX	AREA	AGE	DIAGNOSIS	STAGE	DM	HTN	SMOKING	TREATMENT PLAN	THYROID DOSE	chemo	surg	hypo	BEFORE TREAEMEN			6 WEEKS LATER			19 WEEKS LATER			32 WEEKS LATEF		
														tsh	T4	FTC	TSH	T4	FTC	TSH	T4	FTC	TSH	T4	FTC
1	M	H	60	LARYNX	2	N	Y	Y	PARLLEL OPPOSED LATERAL	5946.444	N	N	YES	1.79	8.60	1.10	0.63	8.60	1.10	17.12	6.10	0.68			
3	F	C	32	ORAL CAVITY	3	N	Y	N	PARLLEL OPPOSED LATERAL	6369.154	Y	Y	YES	3.02	12.30	1.02	9.75	7.70	0.76						
4	M	C	56	LARYNX	1	N	N	N	PARLLEL OPPOSED LATERAL	5377.15	N	N	NO	1.55	7.00	0.50	1.14	8.10	0.94	2.36	7.70	0.93			
6	M	C	68	LARYNX	4	N	N	Y	PARLLEL OPPOSED LATERAL	5619.036	Y	N	NO	1.56	4.50	1.02	1.26	4.50	1.05	2.91	3.60	0.79	2.64	3.20	0.86
8	M	C	48	LARYNX	2	N	N	N	PARLLEL OPPOSED LATERAL	6803.808	N	N	NO	0.59	11.40	1.31	1.12	8.00	1.00	1.84	6.00	0.80	2.45	7.50	1.24
10	M	C	54	ORAL CAVITY	3	N	N	Y	PARLLEL OPPOSED LATERAL	5527.132	N	Y	NO	1.35	7.90	0.80	0.67	7.90	0.80	2.25	7.60	0.92			
12	M	C	58	OROPHARYNX	3	N	N	Y	PARLLEL OPPOSED LATERAL	5190.4	Y	N	NO	2.27	8.40	0.83	1.07	8.00	1.03	1.27	9.50	0.99	2.19	9.90	1.28
13	M	C	60	LARYNX	3	N	Y	N	SMALL FIELDS	4041.184	Y	N	NO	2.24	10.00	1.11	1.23	8.80	1.07	4.26	8.00	1.12	3.44	8.70	1.19
14	M	H	51	OROPHARYNX	4	N	N	Y	PARLLEL OPPOSED LATERAL	3216.708	Y	N	NO	1.40	8.20	1.12	1.43	8.00	1.10						
16	M	C	60	OROPHARYNX	4	N	N	N	PARLLEL OPPOSED LATERAL	5141.924	Y	N	NO	1.37	11.00	1.03	2.10	10.20	0.89	4.21	8.30	1.10			
17	F	C	40	ORAL CAVITY	4	N	N	Y	PARLLEL OPPOSED LATERAL	5548.191254	Y	N	YES	3.38	9.90	0.93	8.75	7.90	0.85						
18	M	C	47	LARYNX	3	N	Y	Y	PARLLEL OPPOSED LATERAL	2867.82	Y	N	NO	1.53	7.40	0.88	0.76	7.40	0.88	2.27	7.50	0.93	1.41	6.90	0.88
19	M	H	52	LARYNX	4	N	N	Y	CONCOMITTENT BOOST	5839.968	N	N	NO	2.21	10.30	0.95	1.53	8.90	1.00	1.57	8.70	0.98			
20	M	C	45	LARYNX	1	N	N	Y	SMALL FIELDS	3348.128	N	N	NO	0.85	11.10	1.32	1.29	10.40	1.21	1.10	7.20	1.05	1.11	8.50	1.04
22	M	C	69	HYPOPHARYNX	4	Y	Y	N	PARLLEL OPPOSED LATERAL	4279.43	N	N	NO	1.00	9.20	0.90	2.13	10.00	1.03						
23	M	C	60	ORAL CAVITY	1	N	N	N	IMRT	N	N	Y	NO	2.85	9.40	1.24	2.33	9.60	1.29	3.79	6.60	0.94			
25	M	C	64	ORAL CAVITY	4	N	N	N	IMRT	N	Y	N	NO	1.21	7.20	1.03	0.88	9.20	0.83						
26	F	C	55	LARYNX	2	N	N	N	PARLLEL OPPOSED LATERAL	5074.554	Y	N	YES	3.16	7.60	0.81	2.67	8.70	0.93	32.65	6.20	0.77			
27	M	C	44	ORAL CAVITY	4	N	N	Y	PARLLEL OPPOSED LATERAL	4947.974	N	N	NO	2.76	8.20	0.80	1.32	6.20	0.89						
28	M	C	53	ORAL CAVITY	4	N	N	Y	PARLLEL OPPOSED LATERAL	6006.088	N	Y	NO	1.01	7.10	0.99	2.15	6.20	0.80	2.64	5.80	0.82			
29	M	C	64	LARYNX	1	N	N	N	IMRT	N	N	N	NO	2.15	6.20	0.80	0.36	9.00	1.04	3.83	5.90	0.96			
30	M	C	38	ORAL CAVITY	4	N	N	Y	PARLLEL OPPOSED LATERAL	N	Y	N	NO	1.45	6.80	1.08	1.24	7.10	1.11	1.96	6.80	0.92			
32	F	C	50	HYPOPHARYNX	4	N	N	Y	DIRECT ANT	N	N	N	NO	0.66	10.90	0.31	0.79	10.90	0.31	1.17	9.90	1.16			
33	M	C	74	LARYNX	2	N	N	N	PARLLEL OPPOSED LATERAL	5827.398	N	N	NO	0.89	10.08	1.50	0.22	9.60	1.11						
34	M	C	49	OROPHARYNX	4	Y	Y	Y	PARLLEL OPPOSED LATERAL	5753.582	Y	N	NO	1.93	8.30	0.94	1.55	8.20	0.89	3.14	8.50	0.84			
35	M	C	77	NASOPHARYNX	4	N	N	Y	PARLLEL OPPOSED LATERAL	5585.99	Y	N	NO	1.73	9.90	1.34	3.14	8.50	0.84						
36	M	C	82	LARYNX	2	N	N	N	PARLLEL OPPOSED LATERAL	5878.096	N	N	NO	2.53	6.90	1.05	3.24	6.00	0.80	3.87	5.60	0.80			
35	M	C	48	HYPOPHARYNX	4	N	N	N	PARLLEL OPPOSED LATERAL	5625.396	Y	N	NO	0.08	10.02	1.20	0.48	7.10	0.92	1.97					
40	M	C	49	LARYNX	2	N	N	N	PARLLEL OPPOSED LATERAL	4884.388	N	N	NO	3.12	7.60	1.06	1.06	7.60	1.00	1.18	7.90	1.13			
42	F	C	51	HYPOPHARYNX	4	N	N	N	DIRECT ANT	3314.07	Y	N	NO	1.38	10.80	1.08	3.14	6.70	0.87						
43	M	C	56	LARYNX	1	N	N	N	SMALL FIELDS	2773.904	N	N	NO	3.02	8.30	0.97	2.75	9.20	1.04						
44	M	C	54	LARYNX	3	N	N	Y	PARLLEL OPPOSED LATERAL	5307.04484	Y	N	NO	2.22	6.40	0.87	2.26	6.50	0.92						
45	M	C	71	LARYNX	2	N	N	Y	SMALL FIELDS	3023.048	N	N	NO	0.54	9.70	1.19	2.43	5.70	0.86						
46	M	H	45	LARYNX	3	N	N	Y	PARLLEL OPPOSED LATERAL	4585.958842	Y	N	NO	0.01	8.30	1.32	1.06	4.80	0.85						
47	M	C	59	HYPOPHARYNX	4	N	N	Y	PARLLEL OPPOSED LATERAL	4561.711999	Y	N	NO	0.50	6.50	0.80	3.38	5.80	0.80						
48	M	C	60	HYPOPHARYNX	1	N	N	N	IMRT	N	Y	N	NO	0.81	10.50	0.98	0.84	10.00	0.96						
50	M	C	56	HYPOPHARYNX	4	N	N	Y	DIRECT ANT	4614.05362	Y	N	YES	4.20	7.80	1.07	12.89	6.00	0.87						

FACT SCORE DATA of all recruited patients

	initial						end of rt						fu-1						fu-2						fu-3			
srl no	phys	social	emot	funct	H&N	total	phy	soci	emot	func	H&N	total	physi	social	emot	func	H&N	total	no	physi	social	emot	func	H&N	total	physi	social	emot	func	H&N	total
1	19	28	15	16	36	114	21	17	17	13	29	97	25	28	14	14	27	108	1	27	28	21	10	45	131	z	z	z	z	z	0
2	14	15	12	10	29	80	18	21	14	13	35	101	x	x	x	x	x	0	2	x	x	x	x	x	x	x	x	x	x	x	0
3	14	28	8	14	22	86	15	28	12	14	22	91	20	28	14	9	28	99	3	z	z	z	z	z	z	z	z	z	z	z	z
4	13	28	11	14	34	100	18	21	17	13	21	90	21	16.8	15.6	6	26	85.4	4	24	28	21	17	36	126	x	x	x	x	x	x
5	11	14	8	6	26	65	13	10.5	14	9	21	67.5	x	x	x	x	x	0	5	x	x	x	x	x	x	x	x	x	x	x	x
6	12	28	6	10	35	91	12	28	15	10	22	87	22	28	15	17	30	112	6	16	28	16	24	36	120	x	x	x	x	x	x
7	13	24.5	12	11	35	95.5	16	25.6	13	13	29	96.6	x	x	x	x	x	0	7	x	x	x	x	x	x	x	x	x	x	x	x
8	13	28	11	13	38	103	15	28	13	13	28	97	21	28	9	11	24	93	8	24	28	14	15	30	111	26	28	15	15	28	112
9	11	28	7	6	29	81	15	28	12	8	28	91	14	28	14	9	36	101	9	12	21	10	5	28	76	x	x	x	x	x	0
10	19	28	15	16	36	114	12	21	8	12	25	78	16	28	11	15	29	99	10	18	28	12	12	32	102	12	21	6	7	26	72
11	21	21	13	15	36	106	15	26.6	16	10	27	94.6	24	28	14	19	35	120	11	28	28	24	25	45	150	28	28	24	26	44	150
12	17	28	11	12	34	102	9	28	5	5	28	75	24	28	16	17	37	122	12	x	x	x	x	x	x	x	x	x	x	x	x
13	14	21	6	6	29	76	12	21	10	8	25	76	x	x	x	x	x	0	13	x	x	x	x	x	x	x	x	x	x	x	x
14	20	19.8	11	6	32	88.8	16	19.8	10	7	20	72.8	24	25.6	16	18	36	119.6	14	x	x	x	x	x	x	x	x	x	x	x	x
15	20	28	8	13	27	96	7	28	2	3	23	63	22	28	11	0	35	96	15	z	z	z	z	z	z	z	z	z	z	z	z
16	20	14	4	7	32	77	19	14	9	9	34	85	27	14	16	16	35	108	16	28	21	18	20	38	125	28	28	24	28	44	152
17	21	28	12	12	32	105	19	28	15	13	28	103	26	28	17	19	37	127	17	25	21	16	20	41	123	x	x	x	x	x	x
18	20	25.7	10	9	34	98.7	13	25.7	10	9	26	83.7	23	22.2	17	18	37	117.2	18	28	28	20	16	34	126	28	28	18	17	33	124
19	20	28	10	12	32	102	16	28	10	11	27	92	26	28	20	20	37	131	19	x	x	x	x	x	x	x	x	x	x	x	x
20	25	28	21	13	38	125	20	28	21	9	27	105	26	28	20	20	37	131	20	28	28	24	27	47	154	x	x	x	x	x	x
21	13	11.7	4	6	25	59.7	22	9.3	16	8	23	78.3	x	x	x	x	x	0	21	x	x	x	x	x	x	x	x	x	x	x	x
22	20	21	14	8	38	101	22	25.6	12	10	30	99.6	24	28	15	12	36	115	22	x	x	x	x	x	x	x	x	x	x	x	x
23	18	21	9	11	38	97	14	21	12	8	33	88	20	21	15	10	36	102	23	22	21	11	6	38	98	z	z	z	z	z	z
24	13	11.7	4	6	25	59.7	22	9.3	16	8	23	78.3	25	17.5	15	15	32	104.5	24	x	x	x	x	x	x	x	x	x	x	x	x
25	18	21	10	12	27	88	18	21	16	14	20	89	23	28	16	20	28	115	25	24	21	15	19	33	112	x	x	x	x	x	x
26	19	21	12	13	39	104	17	25.6	18	11	26	97.6	25	28	18	19	35	125	26	22	21	15	21	38	117	x	x	x	x	x	x

	initial						end of rt						fu-1							fu-2						fu-3					
	phys	social	emot	funct	H&N	total	phy	soci	emot	func	H&N	total	physi	social	emot	func	H&N	total		physi	social	emot	func	H&N	total	physi	social	emot	func	H&N	total
27	12	21	12	13	36	94	18	21	10	10	28	87	19	21	14	12	34	100	**27**	19	25.6	15	12	32	104	x	x	x	x	x	x
28	7	17.5	6	11	19	60.5	15	14	12	9	16	66	17	14	13	14	27	85	**28**	22	28	16	10	30	106	x	x	x	x	x	x
29	21	21	13	15	38	108	15	21	10	10	24	80	17	24	14	15	30	100	**29**	x	x	x	x	x	x	x	x	x	x	x	x
30	11	11.2	2	4	31	59.2	12	11.6	9	9	32	73.6	19	25.6	14	15	35	108.6	**30**	22	28	17	14	38	119	x	x	x	x	x	x
31	14	21	13	9	26	83	12	28	14	12	30	96	15	28	16	18	34	111	**31**	x	x	x	x	x	x	x	x	x	x	x	0
32	24	28	12	15	40	119	21	28	12	12	31	104	26	28	17	18	36	125	**32**	25	28	16	20	35	124	x	x	x	x	x	0
33	20	28	8	6	35	97	14	21	13	8	30	86	x	x	x	x	x	0	**33**	x	x	x	x	x	x	x	x	x	x	x	0
34	26	25.6	12	21	29	113.6	x	x	x	x	x	0	x	x	x	x	x	0	**34**	x	x	x	x	x	x	x	x	x	x	x	x
35	20	28	12	14	43	117	19	28	15	13	23	98	22	21	16	14	28	101	**35**	x	x	x	x	x	x	x	x	x	x	x	x
36	20	28	12	14	43	117	19	28	15	13	23	98	24	28	12	20	32	116	**36**	22	28	15	16	38	119	24	28	16	18	41	127
37	16	28	7	13	30	94	14	28	12	10	28	92	18	28	14	18	36	114	**37**	x	x	x	x	x	x	x	x	x	x	x	x
38	20	21	6	12	32	91	21	28	8	10	28	95	22	21	12	12	30	97	**38**	x	x	x	x	x	x	x	x	x	x	x	x
39	19	16.3	7	9	38	89.3	17	25.6	5	8	30	85.6	22	21	8	15	34	100	**39**	x	x	x	x	x	x	x	x	x	x	x	x
40	19	21	11	15	35	101	16	21	12	12	33	94	18	25.6	15	16	38	112.6	**40**	x	x	x	x	x	x	x	x	x	x	x	x
41	17	11.6	5	20	33	86.6	14	11.6	6	16	35	82.6	17	21	10	18	35	101	**41**	x	x	x	x	x	x	x	x	x	x	x	x
42	18	14	10	10	33	85	16	16.3	12	8	30	82.3	21	28	13	17	36	115	**42**	x	x	x	x	x	x	x	x	x	x	x	x
43	16	28	15	11	29	99	18	28	14	10	25	95	16	28	9	14	28	95	**43**	x	x	x	x	x	x	x	x	x	x	x	x
44	17	28	6	14	32	97	15	28	4	18	28	93	x	x	x	x	x	0	**44**	x	x	x	x	x	x	x	x	x	x	x	x
45	20	25.6	8	10	28	91.6	16	28	6	16	24	90	17	28	10	8	30	93	**45**	x	x	x	x	x	x	x	x	x	x	x	x
46	18	25.6	13	15	38	109.6	16	25.6	12	14	32	99.6	x	x	x	x	x	0	**46**	x	x	x	x	x	x	x	x	x	x	x	x
47	24	28	12	16	41	121	19	28	8	10	28	93	x	x	x	x	x	0	**47**	x	x	x	x	x	x	x	x	x	x	x	x

Thyroid questionnaire data for all recruited patients

S.no	FATIUGE				WEIGHT GAIN				CONSTIPATION				DRY SKIN				COLD INTOLARANCE				TEMPER				APETITE				JOINT PAIN			
	initial	end	FU 1	FU-2	FU 3	initial	END	FU 1	FU-2	FU 3	initial	END	FU 1	FU-2	FU 3	initial	END	FU 1	FU-2	FU 3	initial	END	FU 1	FU-2	FU 3	initial	END	FU 1	FU-2	FU 3	initial	END	FU 1	FU-2	FU 3
1	0	1	0	0	x	0	0	1	x	0	0	1	0	0	x	0	0	0	1	x	0	0	0	x	0	1	0	0	x	0	0	0	0	x
2	0	1	x	x	x	0	0	x	x	x	1	1	x	x	x	0	1	x	x	x	0	1	x	x	x	0	1	x	x	x	0	0	x	x	x
3	0	1	1	x	x	0	0	1	x	x	0	0	1	x	x	0	1	x	x	x	0	1	1	x	x	0	0	0	x	x	0	0	0	x	x
4	0	1	0	0	x	0	0	1	0	x	0	1	0	0	x	0	0	0	0	x	0	0	0	0	x	0	1	0	0	x	0	0	0	0	x
5	1	1	x	x	x	0	0	x	x	x	0	1	x	x	x	0	0	x	x	x	0	0	x	x	x	0	1	x	x	x	0	0	x	x	x
6	0	1	1	1	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	1	0	0	0	1	1	0	0	0	0	0	0	0
7	0	1	x	x	x	0	0	x	x	x	0	0	x	x	x	0	1	x	x	x	0	1	x	x	x	0	1	x	x	x	0	0	x	x	x
8	0	0	1	1	1	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	1	1	0	0	x	0	0	1	0	x	0	1	0	0	x	0	0	0	0	x	0	0	0	0	x	0	1	0	0	x	0	0	0	0	x
10	0	1	1	1	1	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
11	0	1	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	1	1	1
12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	1	1	1
13	0	0	x	x	x	0	0	1	x	x	0	0	x	x	x	0	0	x	x	x	0	0	x	x	x	0	0	x	x	x	0	0	x	x	x
14	0	1	0	0	x	0	0	x	x	x	0	0	x	x	x	0	0	x	x	x	0	0	x	x	x	0	1	x	x	x	0	0	x	x	x
15	0	1	1	x	x	0	0	x	x	x	0	1	0	x	x	0	0	0	0	x	0	0	1	1	x	0	1	0	x	x	0	0	0	x	x
16	0	0	0	0	x	0	0	0	0	x	0	1	0	0	x	0	0	0	0	x	0	0	0	0	x	0	1	0	0	x	0	0	0	0	x
17	0	0	0	0	x	0	0	0	0	x	0	0	0	0	x	0	0	0	0	x	0	0	0	0	x	0	1	0	0	x	0	0	0	0	x
18	0	0	0	0	x	0	0	0	0	x	0	1	0	0	x	0	0	0	0	x	0	0	0	0	x	0	1	0	0	x	0	0	0	0	x
19	0	0	0	0	x	0	0	0	0	x	0	1	0	0	x	0	0	0	0	x	0	0	0	0	x	0	1	0	0	x	0	0	0	0	x
20	0	0	0	0	x	0	0	0	0	x	0	0	0	0	x	0	0	0	0	x	0	0	0	0	x	0	0	0	0	x	0	0	0	0	x
21	0	0	x	x	x	0	0	x	x	x	0	1	x	x	x	0	0	x	x	x	0	0	x	x	x	0	1	x	x	x	0	0	x	x	x
22	0	1	0	x	x	0	0	x	x	x	0	1	x	x	x	0	0	x	x	x	0	0	x	x	x	0	1	x	x	x	0	0	x	x	x
23	1	1	0	1	x	0	0	1	x	x	0	1	0	0	x	0	0	0	1	x	0	0	0	0	x	0	1	0	0	x	0	0	0	0	x
24	0	0	0	X	x	0	0	X	x	x	0	1	0	X	x	0	0	0	X	x	0	0	0	X	x	1	1	0	X	x	0	0	X	X	x
25	0	0	0	0	x	0	0	0	0	x	0	1	0	0	x	0	0	0	0	x	0	0	0	0	x	0	1	0	0	x	0	0	0	0	x
26	0	0	0	0	x	0	0	1	0	x	0	1	0	0	x	0	0	0	0	x	0	0	0	0	x	0	1	0	0	x	0	0	0	0	x
27	0	0	0	0	x	0	0	1	0	x	0	1	0	0	x	0	0	0	0	x	0	0	0	0	x	0	1	0	0	x	0	0	0	0	x
28	0	0	0	0	x	0	0	0	0	x	0	0	0	0	x	0	0	0	0	x	0	0	0	0	x	0	1	0	0	x	0	0	0	0	x
29	0	0	0	0	x	0	0	1	0	x	0	0	0	0	x	0	0	0	0	x	0	0	0	0	x	0	1	0	0	x	0	0	0	0	x
30	0	1	0	0	x	1	1	1	0	x	0	0	0	0	x	1	1	0	0	x	0	0	0	0	x	0	1	0	0	x	0	0	0	0	x
31	0	0	0	X	x	0	0	0	X	x	0	1	0	X	x	0	0	0	X	x	0	0	0	X	x	0	1	0	X	x	0	0	0	X	x
32	0	0	0	0	x	0	0	0	0	x	0	0	0	0	x	0	0	0	0	x	0	0	0	0	x	0	1	0	0	x	0	0	0	0	x
33	0	0	x	x	x	0	0	x	x	x	0	0	x	x	x	0	0	x	x	x	0	0	x	x	x	0	1	x	x	x	0	0	x	x	X
34	0	x	x	x	x	0	x	x	x	x	0	x	x	x	x	0	x	x	x	x	0	x	x	x	x	0	1	x	x	x	0	x	x	x	x
35	0	0	0	0	x	0	1	0	0	x	0	1	0	0	x	0	0	0	0	x	0	0	0	0	x	1	1	0	0	x	0	0	0	0	x
36	0	0	0	0	x	0	0	0	0	x	0	0	0	0	x	0	0	0	0	x	0	0	0	0	x	1	1	0	0	x	0	0	0	0	x
37	0	0	x	x	x	0	1	0	x	x	0	1	0	x	x	0	0	x	x	x	0	0	x	x	x	0	1	x	x	x	0	0	x	x	x
38	0	0	x	x	x	0	1	0	x	x	0	1	0	x	x	0	0	x	x	x	0	0	x	x	x	0	1	x	x	x	0	0	x	x	x
39	0	0	0	0	x	0	1	0	0	x	0	1	0	0	x	0	0	0	0	x	0	0	0	0	x	0	1	0	0	x	0	0	0	0	x
40	0	1	0	x	x	0	0	0	x	x	0	1	0	x	x	0	0	0	x	x	0	0	0	x	x	0	1	0	x	x	0	0	0	x	x
41	0	0	0	x	x	0	1	0	x	x	0	0	0	x	x	0	0	0	x	x	0	0	0	x	x	0	1	0	x	x	0	0	0	x	x
42	0	**0**	**0**	x	x	0	1	0	x	x	0	0	0	x	x	0	0	0	x	x	0	0	0	x	x	0	1	0	x	x	0	0	0	x	x
43	1	1	0	x	x	0	1	0	x	x	0	0	0	x	x	0	0	0	x	x	0	0	0	x	x	1	1	0	x	x	0	0	0	x	x
44	1	1	x	x	x	0	x	x	x	x	0	x	x	x	x	0	x	x	x	x	0	x	x	x	x	1	1	x	x	x	0	x	x	x	x
45	0	1	1	x	x	0	1	0	x	x	0	0	0	x	x	0	0	0	x	x	0	0	0	x	x	1	1	1	x	x	0	0	0	x	x
46	0	1	x	x	x	0	0	x	x	x	0	0	x	x	x	0	0	x	x	x	0	0	x	x	x	1	1	x	x	x	0	0	x	x	x
47	1	0	x	x	x	0	0	x	x	x	0	0	x	x	x	0	0	x	x	x	0	0	x	x	x	0	0	x	x	x	0	0	x	x	x