OCCURRENCE OF HYPOTHYROIDISM IN PATIENTS TREATED FOR HEAD AND NECK CANCER

By

Dr. SMITHA T M

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SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH

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In partial fulfilment of the requirements for the degree of

MASTER OF SURGERY IN OTORHINOLARYNGOLOGY

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TAMAKA, KOLAR

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Place: Signature of the Candidate

LIST OF ABBREVIATIONS

T_3	⇨	Tri-iodo thyronine
T_4	⇨	Tetra-iodo thyronine
TSH	⇨	Thyroid Stimulating Hormone
Tg	⇨	Thyroglobulin
TPO	⇨	Thyroid peroxidase
TRH	⇨	Thyrotrophin Releasing Hormone
BMR	⇨	Basal Metabolic Rate
VA	⇨	Vaterans Affair
AJCC	⇨	American Joint Committee on Cancer
EORTC	⇨	European organization for Research ant Treatment for Cancer
MACH-NC	⇨	Meta analysis of chemotherapy in Head and Neck cancer
RTOG	⇨	Radiation Therapy Oncology Group
EBRT	⇨	External Beam RadioTherapy
RIHT	⇨	Radiation Induced Hypothyroidism

ABSTRACT

BACKGROUND:

Head and Neck cancers account for about 30% of all cancers in India. Surgery , radiation and chemotherapy are the standard of care in these patients, either as a single modality or as a combined modality. Advances in treatment of Head and Neck cancers are helping us achieve better locoregional control in the recent days, this at a cost of post treatment sequelae. One such sequelae is hypothyroidism. In literature there is variable incidence of hypothyroidism ranging from 8-67% in Head and Neck cancer patients treated by different modalities. There is paucity of prospective studies dealing with the incidence and onset of hypothyroidism in patients treated for Head and Neck cancer, hence this study is done.

OBJECTIVES:

1) To determine pre and post treatment serum thyroid hormone levels in patients undergoing treatment for Head and Neck cancer

2) To document the frequency of occurrence and onset of hypothyroidism by periodic thyroid hormone assay in patients who are undergoing treatment for Head and Neck cancer.

METHOD:

Ours is a prospective observational study done between December 2013 to July 2015 at R L Jallappa Hospital and Research centre, Tamaka, Kolar to find out the frequency and onset of hypothyroidism in patients treated for Head and Neck cancer by testing the thyroid function tests of the patients during pretreatment and at three months, six months and one year (where ever possible) in the follow up period. Totally ninety patients were included in the study. The patients underwent treatment for various Head and Neck cancer either by

single or multimodality treatment with surgery, radiotherapy and/or chemotherapy. For all patients thyroid function tests was done pretreatment and at regular intervals in the follow up period (three months, six months and one year wherever possible.

RESULTS:

At the end of three months three patients, at the end of six months seven patients and at the end of one year nine patients developed hypothyroidism. There was statistically significant change in TSH values at three months, six months and one year compared to pretreatment values. The incidence of hypothyroidism is more in male patients. Majority of patients had subclinical hypothyroidism (n=7).

CONCLUSION:

The overall incidence of hypothyroidism at the end of six months is 8% and 16% at the end of one year. The incidence of subclinical hypothyroidism is more compared to clinical hypothyroidism hence thyroid function tests are advised at regular intervals for all head and neck cancer patients in the follow up period.

KEY WORDS: Hypothyroidism, Head and Neck cancer, Thyroid function tests

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Introduction

INTRODUCTION

Head and Neck cancers account for about 30% of all cancers in India.[1] Surgery , radiation and chemotherapy are the standard of care in these patients, either as a single modality or as a combined modality.

Advances in treatment of Head and Neck cancers are helping us achieve better locoregional control in the recent days, this at a cost of post treatment sequelae. One such sequelae is hypothyroidism.

In literature there is variable incidence of hypothyroidism ranging from 8-67% in Head and Neck cancer patients treated by different modalities.[2,3,4,5,6]

Hypothyroidism can have a significant impact on the healing and also on the quality of life in Head and Neck cancer patients. The routine clinical features of hypothyroidism can be masked by the disease and treatment.

There is paucity of prospective studies dealing with the incidence and onset of hypothyroidism in patients treated for Head and Neck cancer, hence this study is done.

Aims & Objectives

AIMS AND OBJECTIVES

RESEARCH HYPOTHESIS:

The Head and Neck cancer patients may develop hypothyroidism in the post treatment period.

RESEARCH QUESTION:

Do patients treated for Head and Neck cancer develop hypothyroidism over a period of time.

AIMS AND OBJECTIVES:

1) To determine pre and post treatment serum thyroid hormone levels in patients undergoing treatment for Head and Neck cancer
2) To document the frequency of occurrence and onset of hypothyroidism by periodic thyroid hormone assay in patients who are undergoing treatment for Head and Neck cancer.

Review of Literature

REVIEW OF LITERATURE

BRIEF HISTORICAL REVIEW:

Thyroid gland was first identified in 1656 by the anatomist Thomas Wharton and named the gland as thyroid, meaning shield as its shape resembled the shields commonly used in Ancient Greece.[7]

Theodor Kocher got Nobel Prize in Medicine "for his renowned work on physiology, pathology and surgery of the thyroid gland" in the year 1909.[7]

EMBRYOLOGY

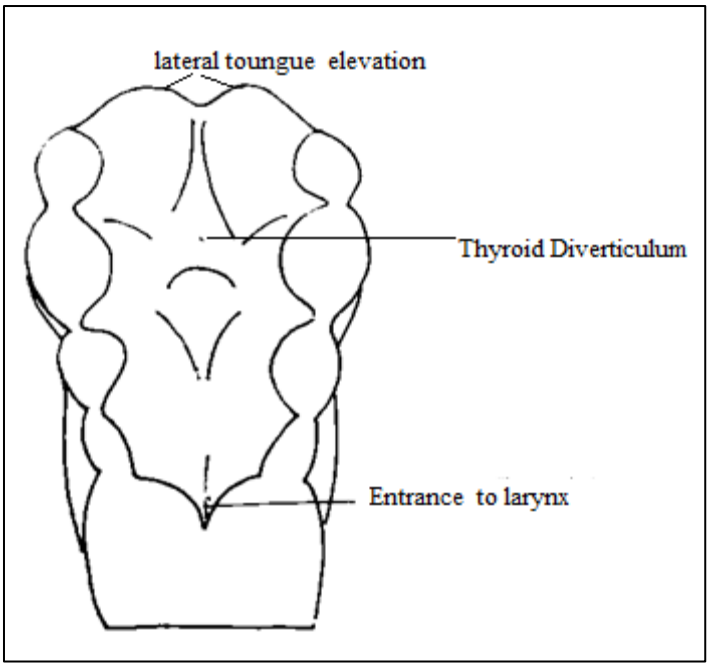


Figure-1: Floor of pharynx in 18 to 21 days old embryo

Thyroid gland appears as an epithelial proliferation in the floor of the pharynx at the base of the tongue between the tuberculum impar and the copula linguae at a point later indicated by the foramen cecum during 3–4 weeks of gestation. Then it

descends through the thyroglossal duct in front of the pharyngeal wall as a bilobed diverticulum. Production of thyroxine (T_4) reach a clinically significant level at the age of 18–20 weeks of intra uterine life. Triiodothyronine (T_3) remains low (less than 15 ng/dL) until 30 weeks of gestation, and increases to 50 ng/dL at term.[7]

Thyroid gland also contains parafollicular or_C cells, which produces calcitonin and are derived from which in turn derived from neural crest cells. Ultimobranchial body joins the primordial thyroid gland during its descent to its final location in the anterior neck around 18–20 days of gestation.[7]

GROSS ANATOMY

The thyroid the largest endocrine gland in human body, which weighs around 2-3 grams in neonates and 18-60 grams in adults. It is Butterfly in shaped and comprises of two cone-like lobes right and left connected by isthmus. Each lobe measures around 5 cm long, 3 cm wide and 2 cm thick. The thyroid is situated on the anterior part of the neck, around the larynx and trachea, reaching posteriorly to the esophagus and carotid sheath. Cranially the gland extends up to the oblique line on the thyroid_cartilage (just below the laryngeal prominence, or 'Adam's Apple'), and inferiorly it extends upto fifth or sixth tracheal ring. It is difficult to demarcate the gland's upper and lower border with vertebral levels because it moves in relation to these during swallowing. Around 28%-55% of population have third lobe called the pyramidal lobe which is conical in shape and extends from the upper part of the isthmus to the hyoid bone. The pyramidal lobe is a remnant of the fetal thyroid stalk or thyroglossal duct.[7]

The gland is covered by a thin fibrous capsule, which is composed of two layers an internal and an external layer. The external layer is continuous anteriorly with the pre tracheal fascia and posteriolaterally continuous with the carotid sheath. The gland is covered anteriorly with infrahyoid muscles and laterally with the sternocleidomastoid muscle. On the posterior aspect, the gland is fixed to the cricoid and tracheal cartilage and cricopharyngeal muscle by a thickening of the fascia to form the posterior suspensory ligament of thyroid gland also known as Berry's ligament. Two parathyroid glands are present on posterior side of the each lobes between the two layers of the capsule.[7]

The thyroid gland is supplied by superior thyroid artery, a branch of the external carotid artery, and the inferior thyroid artery, a branch of the thyrocervical trunk, and sometimes by the thyroid ima artery, a branch directly from the subclavian artery. The venous drainage via superior thyroid veins drains to internal jugular vein, and through inferior thyroid veins to brachiocephalic vein.[7]

Lymphatic drains frequently to the lateral deep cervical lymph nodes and to the pre- and paratracheal lymph nodes. The gland is supplied by parasympathetic nerve input from the superior laryngeal nerve and the recurrent laryngeal nerve.[7]

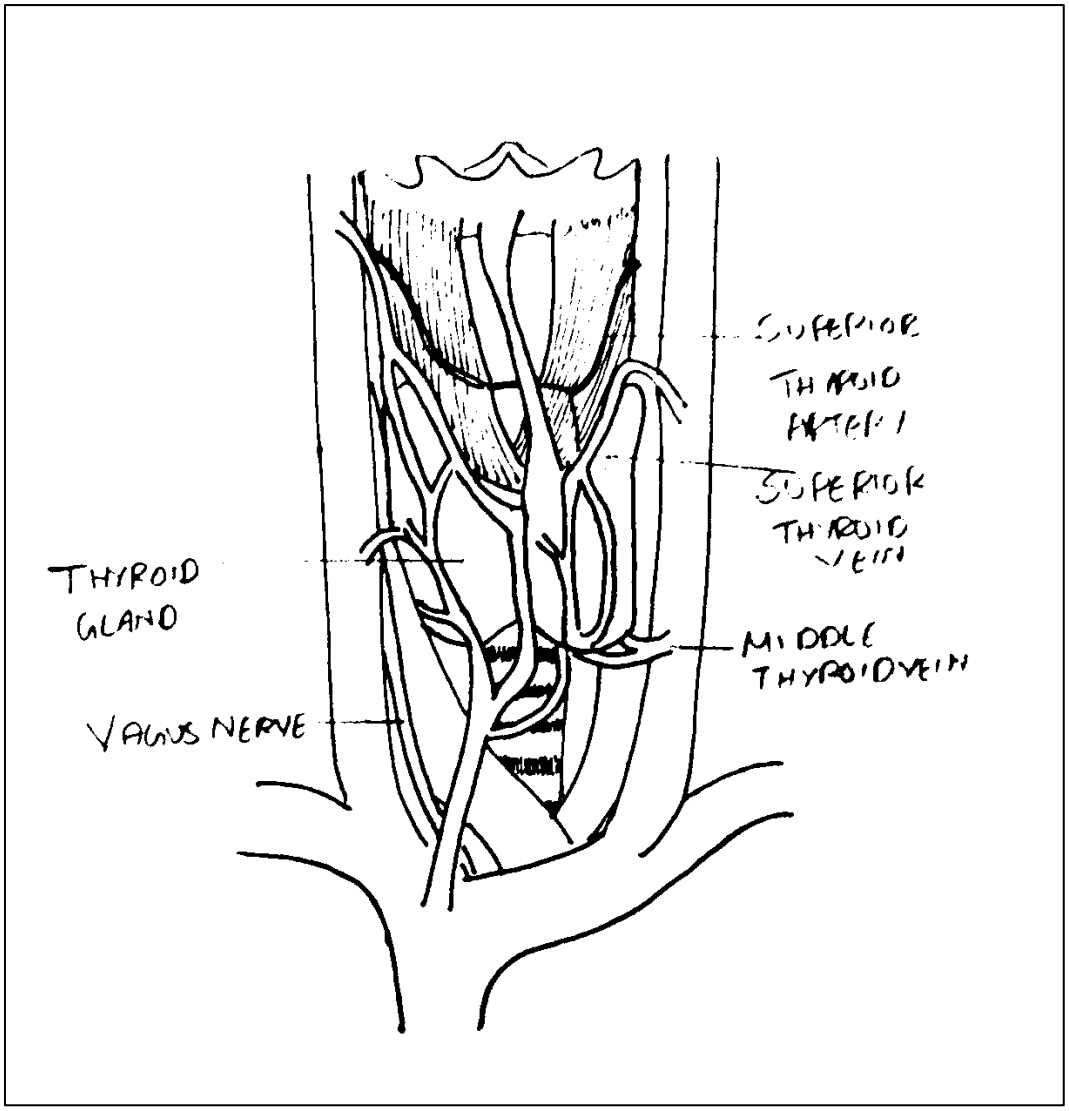


Figure-2: Anatomical relations, vascular supply and lymphatic drainage of thyroid gland

HISTOLOGY

Histologically there are three primary characteristics in thyroid gland, first described by Geoffary Websterson in 1664.

Feature	Description
Follicles	The thyroid is composed of spherical follicles that selectively absorb iodine (as iodide ions, I^-) from the blood for production of thyroid hormones, and also for storage of iodine in thyroglobulin. Twenty-five percent of the body's iodide ions are in the thyroid gland. In follicular lumen, colloid is rich in a protein thyroglobulin which is a reservoir of materials for thyroid hormone production and, to a lesser extent, as a reservoir for the hormones themselves.[7]
Thyroid epithelial cells (or"follicular cells")	A single layer of thyroid epithelial cells surrounds the follicles, which secrete T_3 and T_4. When the gland is inactive, structure of the epithelial cells range from low columnar to cuboidal cells. When active, the epithelial cells become tall columnar cells.
Parafollicular cells (or "C cells")	These cells are present in the spaces between the follicles and secretes calcitonin.[7]

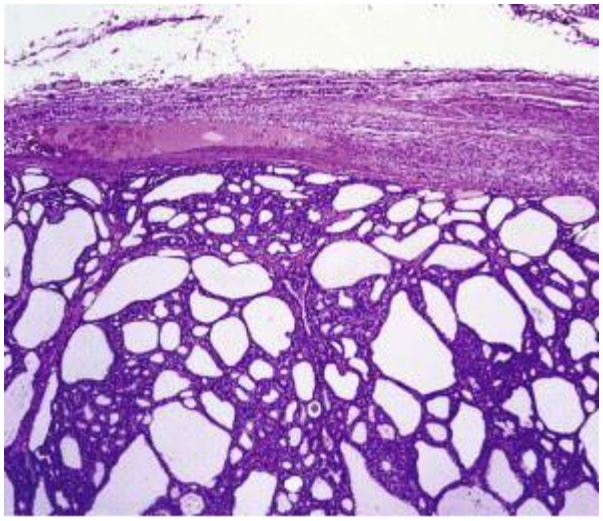


Figure-3: Varying sizes of thyroid follicles along with thyroid capsule.

PHYSIOLOGY

The primary function of the thyroid is production of the hormones T_3, T_4 and calcitonin. Around 80% of the T_4 is converted to T_3 by liver, kidney and spleen. T_3 is more powerful than T_4, which is largely a prohormone, perhaps four or even ten times more active.[8]

T_3 and T_4 production and action

Thyroxine (T_4) is synthesised by the follicular cells from free tyrosine and on the tyrosine residues of the protein called thyroglobulin (Tg). Iodine is captured with the "iodine trap" by the hydrogen peroxide generated by the enzyme thyroid peroxidase (TPO) and linked to the 3' and 5' sites of the benzene ring of the tyrosine residues on Tg, and on free tyrosine.[8] Upon stimulation by the thyroid-stimulating hormone (TSH), the follicular cells reabsorb Tg and cleave the iodinated tyrosines from Tg in lysosomes, forming T_4 and T_3 (in T_3, one iodine atom is less compared to T_4), and releasing them into the blood. Deiodinase enzymes convert T_4 to T_3. Thyroid

hormone secreted from the gland is about 80-90% T_4 and about 10-20% T_3.[6,7] Cells of the developing brain are a major target for the thyroid hormones. Thyroid hormones play a crucial role in brain maturation during fetal development.[9] A transport protein that seems to be important for T_4 transport across the blood–brain barrier (OATP1C1) has been identified. A second transport protein (MCT8) is important for T_3 transport across brain cell membranes.[8]

In the blood, T_4 and T_3 are partially bound to thyroxine-binding globulin (TBG), transthyretin, and albumin. Only a very small fraction of the circulating hormone is free (unbound) - T_4 0.03% and T_3 0.3%. Only the free fraction has hormonal activity. As with the steroid hormones and retinoic acid, thyroid hormones cross the cell membrane and bind to intracellular receptors (α_1, α_2, β_1 and β_2), which act alone, in pairs or together with the retinoid X-receptor as transcription factors to modulate DNA transcription.[8]

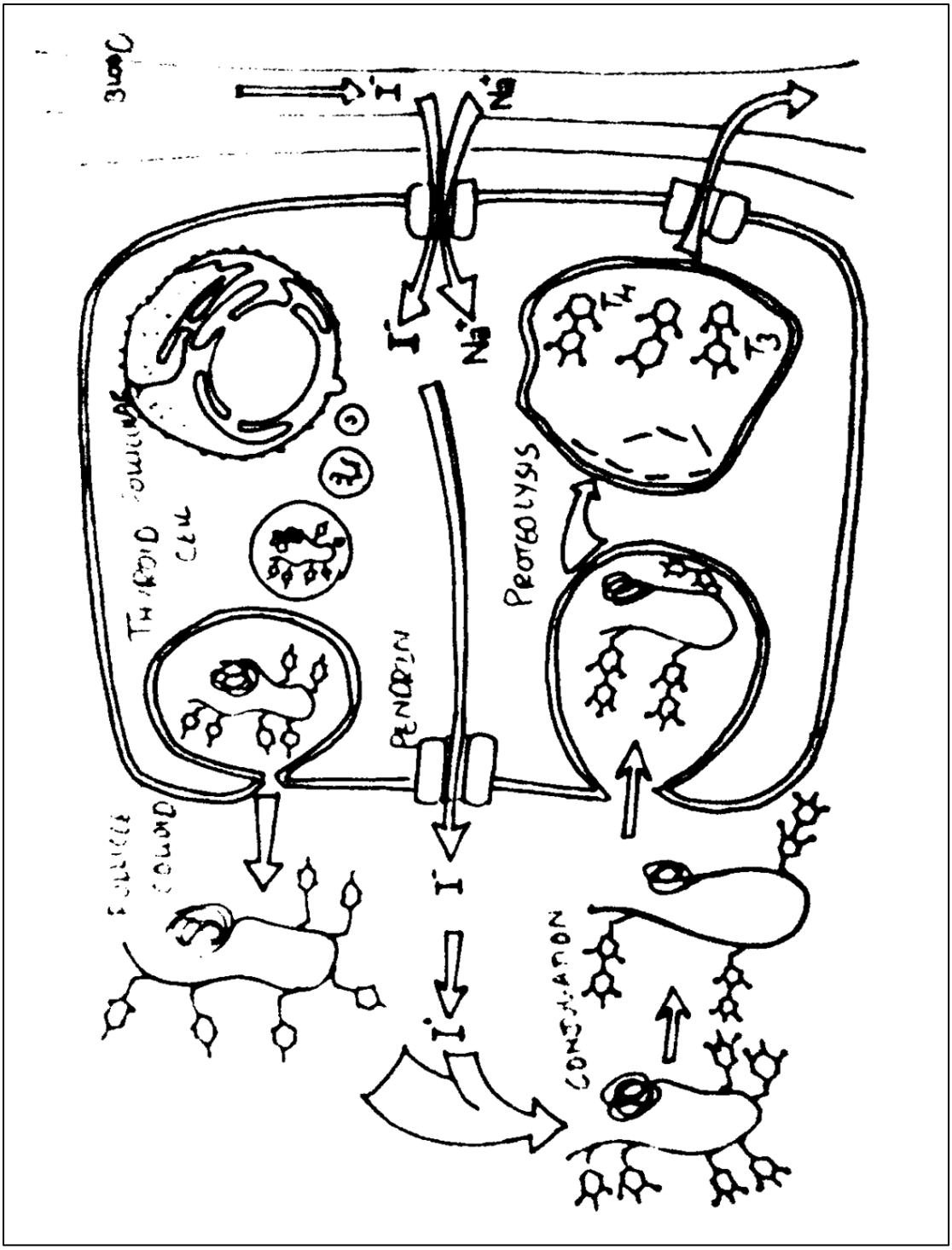


Figure-4: Showing production on action of T3 and T4.

The production of thyroxine and triiodothyronine is regulated by thyroid-stimulating hormone (TSH), released by the anterior pituitary. The thyroid and thyrotropes form a negative feedback loop: TSH production is suppressed when the T_4

levels are high.[12] The TSH production itself is modulated by thyrotropin-releasing hormone (TRH), which is produced by the hypothalamus and secreted at an increased rate in situations such as exposure to cold (to stimulate thermogenesis) TSH production is blunted by somatostatin (SRIH), rising levels of glucocorticoids and sex hormones (estrogen and testosterone), and excessively high blood iodide concentration.[8]

Another hormone calcitonin produced by the thyroid regulates serum calcium levels. Parafollicular cells produce calcitonin in response to hypercalcemia. Calcitonin stimulates uptake of calcium into bone, in opposition to the effects of parathyroid hormone (PTH). Calcitonin seems far less essential than PTH, as calcium metabolism remains clinically normal after removal of the thyroid (thyroidectomy), but not the parathyroids. [8]

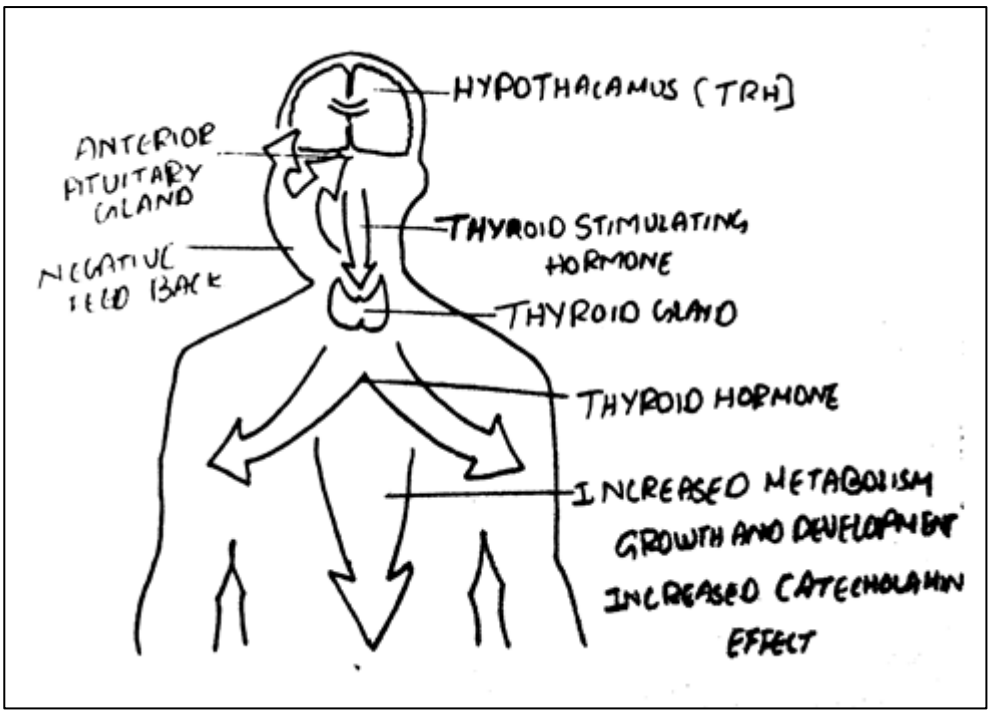


Figure-5: Showing T3 and T4 regulation

Table 1: Normal levels of thyroid hormones[8]

Test	Abbreviation	Normal ranges
Serum thyrotropin/thyroid-stimulating hormone	TSH	0.5–6.0 μU/ml
Serum thyroxine	T_4	6-13 μg/dl
Serum tri iodothyronine	T_3	0.8–1.8 μg/l = 80–180 ng/dl

THYROID HORMONE EFFECTS ON TARGET TISSUES AND METABOLISM

Thyroxine acts by binding to a specific nuclear thyroid hormone receptor (TR). In humans there are two TR genes, alpha and beta. T3 has a 15-fold higher binding affinity for TRs than T4. The hormone receptor complex binds to DNA via zinc fingers and increases/ decreases the expression of a variety of different genes that code for proteins that regulate cell function.[8]

Thyroid hormone is critical for normal bone growth and development. Thyroid hormone increases the level of growth hormone and insulin like growth factor and there by helps in growth.[8]

Basal metabolic rate: Thyroid hormone increases the consumption of oxygen in various tissues in the body. Thyroid hormone increases the metabolic activity in the cells by activating and increasing the number of mitochondria, where most of the metabolic cycles takes place. It increases the expression of uncoupling protein and thus there will be conversion of potential energy into heat and increase in BMR. It does not increases BMR in brain.[8]

Cardiovascular system -Thyroid hormone lowers systemic vascular resistance, increases blood volume, and has inotropic and chronotropic effects on cardiac function. The combination of these effects on both the circulation and the heart itself results in increased cardiac output.[8]

Adipose tissue- Thyroid hormone plays important roles in the development and function of brown and white adipose tissue.[17] Studies in the adult rat have shown that T3 plays important roles in regulating basal oxygen consumption, fat stores, lipogenesis, and lipolysis. In white adipose tissue, T3 induces key lipogenic enzymes such as acetyl CoA carboxylase, malic enzyme, glucose-6-phosphate dehydrogenase, fatty acid synthase. Additionally, T3 also regulates lipolysis in a coordinate manner with lipogenesis.[8]

Liver -Thyroid hormone has multiple effects on liver function including stimulation of enzymes regulating lipogenesis and lipolysis as well as oxidative processes.[8]

Pituitary- Thyroid hormone regulates the synthesis and secretion of several pituitary hormones. Absence of GH has been observed in the pituitaries of hypothyroid rats. Additionally, T3 can stimulate the transcription of GH mRNA and GH synthesis in rat pituitary tumor cells.[8]

Brain and peripheral nervous system- Thyroid hormone has major effects on the developing brain in utero and during the neonatal period. Neonatal hypothyroidism due to genetic causes and iodine deficiency in humans can cause mental retardation and neurological defects.[8]

HYPOTHYROIDISM

Hypothyroidism is a syndrome charecterised by the clinical and biochemical manifestations of thyroid hormone deficiency in the target tissues of thyroid hormone.[9]

Hypothyroidism can be mainly divided into central hypothyroidism and primary hypothyroidism Central hypothyroidism is reduced secretion of thyroid hormones due to insufficient stimulation of thyroid gland by TSH which is caused by lesions in the pituitary and hypothalamus.

Primary hypothyroidism is due to decreased production of thyroid hormones either due to pathology in the gland itself or because of thyroid autoantibodies.

Primary hypothyroidism accounts for 99% of the cause for hypothyroidism. Primary hypothyroidism is due to destruction of gland by autoimmune disease, congenital defects in thyroid hormone synthesis, iodine defeciency or irradiation involving the gland.

Subclinical hypothyroidism: Hypothyroidism with increased TSH and normal levels of thyroid hormone (T3 and T4) is called subclinical hypothyroidism.

Overt hypothyroidism is increased TSH level with decreased thyroid hormone levels.

Incidence of hypothyroidism varies in different parts of the world.

Hypothyroidism is more in women and in elderly age group. Since thyroid hormone acts on many systems its deficiency affects most of them.[9]

Common symptoms of hypothyroidism[9]

- Arthralgias
- Cold intolerance
- Constipation
- Depression
- Difficulty concentrating
- Menorrhagia
- Myalgias
- Weakness
- Weight gain
- Dry skin
- Fatigue
- Hair thinning/hair loss
- Memory impairment.

Clinical signs of hypothyroidism[9]

- Bradycardia
- Dry skin
- Coarse facies
- Cognitive impairment
- Delayed relaxation phase of deep tendon reflexes
- Diastolic hypertension
- Oedema
- Goitre
- Hypothermia
- Lateral eyebrow thinning

- Low-voltage electrocardiography
- Macroglossia
- Periorbital oedema
- Pleural and pericardial effusion

Laboratory results in hypothyroidism[9]

- Elevated C-reactive protein
- Hyperprolactinaemia
- Hyponatraemia
- Increased creatine kinase
- Increased low-density lipoprotein cholesterol
- Increased triglycerides
- Normocytic anaemia
- Proteinuria

CAUSES OF HYPOTHYROIDISM[10]

Central hypothyroidism

1) Loss of functional tissue

a) Tumours (pituitary adenoma, craniopharyngioma, meningioma, dysgerminoma, glioma, metastasis)
b) Trauma (surgery, irradiation, head injury)
c) Vascular (ischemic necrosis, hemorrhage, stalk interruptrion, aneurysm of internal carotid artery)
d) Infections (abscess, tuberculosis, syphilis, toxoplasmosis)
e) Infiltrative (sarcoidosis, histiocytosis, hemochromatosis)
f) Chronic lymphocytic hypophysitis
g) Congenital (pituitary hypoplasia, septo-optic dysplasia, basal encephalocele)

2) Functional defects in TSH biosynthesis and release

a) Mutation in genes encoding for TRH receptor, TSHbeta, or pituitary transcription factors.
b) Drugs: dopamine, glucocorticoids, levothyroxine withdrawal, bexarotene.

PRIMARY (THYROIDAL) HYPOTHYROIDISM

1) Loss of functional thyroid tissue

a) Chronic autoimmune thyroiditis
b) Reversible autoimmune hypothyroidism (silent and postpartum thyroiditis, cytokine-induced thyroiditis)
c) Surgery and irradiation (^{131}I or external irradiation)
d) Infiltrative and infectitous diseases, subacute thyroiditis
e) Thyroid dysgenesis

2) Functional defects in thyroid hormone biosynthesis and release

a) congenital defects in thyroid hormone biosynthesis
b) Iodine deficiency and iodine excess
c) Drugs: antithyroid agents, lithium, natural and synthetic goitrogenic chemicals, tyrosine kinase inhibitors

PERIPHERAL HYPOTHYROIDISM

1) Mutation in genes encoding for MCT8, SECISBP2, or TR beta
2) Consumptive hypothyroidism

The effect of hypothyroidism on metabolism and peripheral tissue are[10]

METABOLISM: In hypothyroid state there will be decrease in metabolism which leads to low basal metabolic rate, decreased apetite, cold intolerance and slightly low basal body temperature. There will be reduction in both synthesis and degradation of protein since the degradation of protein is more compared to the synthesis there will be positive nitrogen balance. In hypothyroidism there will be increased permeability of capillaries which results in increased level of protein in effusion and CSF. In hypothyroidism there will be decreased expression of GLUT-4 in the skeletal muscles and decreased gluconeogenesis and at the same time there is reduced degradation of insulin. All these process maintain the level of glucose in the blood. In hypothyroidism like protein there will be decreased synthesis and degradation of lipid in the body but the level of LDL increases in the plasma which is one of the main risk factor for atherosclerosis and heart disease. During fasting and starvation there will be decreased lipolysis in hypothyroidism even for catecholamines.

CATECHOLAMINES: At tissue level there is reduced sensitivity to catecholamines, glucagon and parathyroid hormone. All these hormones acts through cyclic AMP. This shows that thyroid hormone has the function of modulating Camp generation

CARDIOVASCULAR SYSTEM: There will be decrease in cardiac output due to decrease in both stroke volume and heart rate. ECG changes in hypothyroidism are sinus bradycardia, prolongation of the PR interval, low amplitude of the P wave and QRS complex, alterations of the ST segment, flattened and inverted T waves. There will be increase in the levels of homocysteine, creatine kinase, aspartate aminotransferase and lactate dehydrogenase in hypothyroidism. It is also observed that there is increase in the level of total and low density lipoprotein cholesterol in the blood. It has been proved in many studies that hypothyroidism is a risk factor for atherosclerosis and cardiovascular disease.

RESPIRATORY SYSTEM: Diffusion capacity and maximum breathing capacity are reduced in hypothyroidism but the symptom of difficulty in breathing is rare. Due to myxedematous involvement of the respiratory muscles there will be depression in both hypoxic and hypercapnic ventilator drives which will cause alveolar hypoventilation and CO2 retention.

ALIMENTARY SYSTEM: Increase in weight of the body is due to the retention of water by the hydrophilic glycoprotein deposits. There will be decreased peristalysis in hypothyroidism. Constipation in hypothyroidism is due to the decreased peristalysis and decreased apetite. There will be decreased absorption of food. Since autoimmunity is one of the major causes of hypothyroidism many patients also have pernicious anaemia, gluten enteropathy etc It has been observed in primary

hypothyroidism that there will be achlorhydria even after maximal histamine stimulation. In histologic examination there will be atrophy of the gastric and intestinal mucosa.

SKIN AND MUCOSA: There is increased accumulation of hyaluronic acid in the dermis a Glycosaminoglycan. It is hygroscopic in nature and it gives edematous feature to the skin. The skin will be dry and coarse due to decreased secretion from sebaceous and sweat glands. In hypothyroidism the sensitivity of the skin to cold is due to decreased blood supply to skin.

Hair will become lusterless and brittle. There will be increased loss of hair and decreased growth. Under microscopy there will be hyperkeratosis of epithelium and edematous dermis. It also causes enlargement of tongue and laryngeal and pharyngeal mucosa which is the cause of change in voice in hypothyroidism

WOUND HEALING: There will be delayed wound healing in patients with hypothyroidism . Thyroid hormones are required for the synthesis of collagen, in cases of hypothyroidism there will be decreased cross linkage of collagen fibres and under microscopy the collagen fibers are coarse compared to the normal collagen.

The common manifestations of hypothyroidism are slowed mentation, depression, skin dryness, pleural and pericardial effusions, decreased gastrointestinal motility, weight gain and cold intolerance.

In hypothyroidism the potential post treatment complications are decreased wound healing, impaired development of tracheo esophageal speech, pharyngocutaneous fistula, acceleration of atherosclerosis and hypercholesterolemia.

INCIDENCE OF HEAD AND NECK CANCER

Anually 2,00,000 patients are diagnosed with Head and Neck cancer in India and among them 80,000 patients have oral cancers.[11] More than half (57.7%) of the Head and Neck cancer in the World occurs in Asia and majority in India.[12] In India Head and Neck cancer constitutes 30% of all cancers.[1] Squamous cell carcinoma of Head and Neck has high prevalence in and around Kolar District.[13]

TREATMENT MODALITIES IN HEAD AND NECK CANCER

Squamous cell carcinoma account for 90% of cancer in Head and Neck region followed by other malignancies such as sarcoma and lymphoma.[14,15] Head and Neck is a region of anatomical, physiological and functional complexity. Treatment of these cancers can be challenging. Inspite of significant improvement in the various modalities of treatment, the overall survival has not shown a similar improvement. Earlier most of the patients were managed by single modality of treatment of late multidisciplinary team approach is the standard of care. Early malignancies are still managed by single modality of treatment depending on various dictating factors and advanced malignancies are managed by multi modality approach. A marginal improvement of survival is achieved by multidisciplinary treatment at a cost of various morbidities caused due to numerous complications. Surgery, Radiotherapy, Chemotherapy and recently targeted therapy form the main stay of treatment for Head and Neck cancer.

Surgery:

Surgery for Head and Neck cancer addresses the primary tumour and the regional lymphatics. With the advent of free tissue transfer, locally advanced resectable tumours are now amenable for surgery. Surgery can be curative in early stages and curative or palliative in advanced stages. The amount of resection and reconstruction depends on patient and tumour factors. Extensive surgeries are associated with morbidity which can have delayed effects. One such condition is post operative hypothyroidism.[14]

Radiotherapy:

The role of early forms of radiation was masked by the long term effects to surrounding tissue. The newer generation radiation machine tries to achieve more dosage to the tumour/tumour bed and spare the normal tissue. The basic principle of radiotherapy is to focus the maximum dosage to the tumour and its region of spread and reduce the damage to surrounding tissue. Radiation causes cell damage by direct and indirect effect, which can affect normal tissue. Primary RT is used to treat early tumour and regional spread in(N0 and N1) neck with results comparable to surgery. Primary RT is conventionally given in 1.8-2 Gy/day 5 days per week per week for 6-7 week with a cumulative dose of 60-70Gy. Adjuvant radiotherapy, It is used along with surgery when there is a increased risk of locoregional and failure rates. PORT is indicated in case of close margins, lymphovascular invasion, perineural spread, bone spread, soft ttissue spread and extracapsular spread. PORT is usally given in dose of 60-66 Gy. Salvage radiotherapy is used in recurrence. Brachytherapy maximizes radiation dose to the site of tumours and minimizing the dose to surrounding tissue, useful in tumours of oral cavity without bony invasion. Altered fractionation like

hyperfractionation and accelerated fractionation have attempted to reduce the early and late complications of RT and increase the dose to the tumour/tumour bed. Head and Neck squamous cell carcinoma is radioresistant and originates in the region of many radiosensitive organ like brain, eye, spinal cord, thyroid gland predisposing to potential long term effects of radiotherapy.[14]

Chemotherapy:

Chemotherapeutic drugs are used in the treatment of lymphomas and various sarcomas arising in the Head and Neck region. Head and Neck squamous cell carcinoma is resistant to chemotherapy and therefore it is usually used as a adjuvant. The commonly used chemotherapeutic agents used in Head and Neck cancer are ,alkylating agents- cisplatin, carboplatin, oxaliplatin, antimetabolites- 5 FU and Taxanes- paclitaxel, docetaxel. Chemotherapy is used in the neoadjuvant settings in the hope of reducing the tumour volume, eradicating micrometastasis and may help us to understand the biological response of the tumour. Benefits of neoadjuvant chemotherapy was highlighted in the VA study and EORTC studies.[16,17] Concurrent chemoradiotherapy, the rationale of using chemotherapy along with radiotherapy is the synergistic effect they produce. Chemotherapeutic drugs like cisplatin have potential radiosensitizing effect. Concurrent chemoradiotherapy is used in the treatment of many locally advanced head and neck squamous cell carcinoma as a definitive modality of treatment. Significantly higher rates of locoregional control have been documented in various studies like the MACH –NC and RTOG 91-11.[18,19] Adjuvant concurrent chemoradiotherapy is used in tumour with adverse pathological factors like extracapsular spread, positive margins, perineural and lymphovascular spread. But addition of chemotherapy to radiotherapy is associated with increased toxicity requiring expert supportive care and long term follow up.[14]

EFFECT OF SURGERY ON THYROID GLAND

Surgery is_the primary modality of treatment in majority of Head and Neck cancer. The first case of hypothyroidism due to surgical therapy was reported in 1971.[20] The blood supply of thyroid gland is by superior thyroid artery, the first branch of external carotid artery and the inferior thyroid artery a branch of thyrocervical trunk. The blood supply to the thyroid gland can get disturbed by direct manipulation during the surgeries. Surgeries like laryngectomy, pharyngectomy, bilateral neck dissection, central compartment clearance, paratracheal lymph node dissection can hence predispose to the development of postoperative hypothyroidism.[21,22]

There is paucity of studies on incidence of hypothyroidism following neck dissection and studies comparing the incidence of hypothyroidism to the type of neck dissection.[21] Bilateral neck dissection has been associated with a high incidence of post operative hypothyroidism, whereas unilateral neck dissection is not a known risk factor for hypothyroidism.

Inferior thyroid pedicle is at risk during supraclavicular fossa clearance done in patients with nodal metastasis in carcinoma breast, stomach carcinoma and carcinoma prostate. The inferior artery can also get injured during level four and level six lymph node clearance leading to vascular compromise to the gland.[21]

Dissection of level six lymph nodes: includes the removal of all fibrofatty tissue along with the pretracheal and paratracheal lymph nodes between the carotid arteries and the trachea inferiorly upto the superior mediastinum commonly done for advanced laryngeal and hypopharyngeal malignancies. To facilitate the removal of the nodes the ipsilateral thyroid gland need to be sacrificed as metastasis to the

pretracheal and paratracheal nodes is associated with increased local failure and stomal recurrence. There is a high prevalence of level 6 nodal metastasis in case of subglottic cancer (40%), transglottic cancer (21.4%), supraglottic cancer with ventricular spread, paraglottic space involvement (15.8%), T3 and T4 glottic cancer with anterior commissure involvement (12.5%).[21,22]

Laryngeal and hypopharyngeal malignancies are addressed by total laryngectomy. Usually a ipsilateral lobectomy or a total thyroidectomy is performed during total laryngectomy.[23,24,25,26,27] Indication for thyroidectomy during laryngectomy are T3 and T4 lesion, subglottic disease, transglottic growth, anterior commissure involvement and extralaryngeal softtissue involvement.[28,29] Although invasion of the thyroid gland is rare is reported to have a poor prognosis. If it occurs invasion can occur either by contiguous spread or by lymphovascular Invasion.[30] Hypothyroidism has been reported 23-63% of patients who undergo hemithyroidectomy during total laryngectomy. This risk increases to 91% if the patient receives adjuvant radiotherapy.[23,24,31] Even in patients who undergo only total laryngectomy and in whom both the lobes of thyroid are preserved the incidence of hypothyroidism reported is around 20%, this could be due to damage to the vascular pedicle.[24]

In a study the incidence of hypothyroidism following laryngectomy in 182 patients for laryngeal and hypopharyngeal cancer was 52%, the risk factors in the development of hypothyroidism was hemithyroidectomy and adjuvant radiation.[32] The incidence of hypothyroidism in cases of bilateral neck dissection and level six lymph node clearance is 34.5% and 83.3% respectively.[21]

In a population based study, the incidence of hypothyroidism was 39% at the end of ten years in various head and neck cancers treated by surgery alone.[33]

The incidence of hypothyroidism in patients treated by surgery increases whenever adjuvant radiation is given in the postoperative period for better locoregional control and disease free survival.[21]

EFFECT OF RADIATION THERAPY ON THYROID GLAND

The EBRT is a integral part of single/multimodality treatment in Head and Neck cancer. The nontarget tissues and organs will be inevitably exposed even in the most modern form of radiation therapy (RT). The result of radiation exposure to normal tissue may lead to functional consequences that are readily apparent to both patients and clinicians. In 1920 the effects of radiation to thyroid gland was first observed, when radiation was given to thyrotoxicosis patient.[34] In case of external beam radiotherapy, 2625 to 4865 rads was sufficient to cause hypothyroidism in a normal gland.[35] In a normal thyroid gland 30,000 to 40,000 rad of I 131 (radio active iodine) was necessary to completely ablate the gland.[36] The first case of RIHT (Radiation Induced Hypothyroidism) was reported in 1961 after the treatment of laryngeal carcinoma and it was considered as a rare complication of treatment.[37]

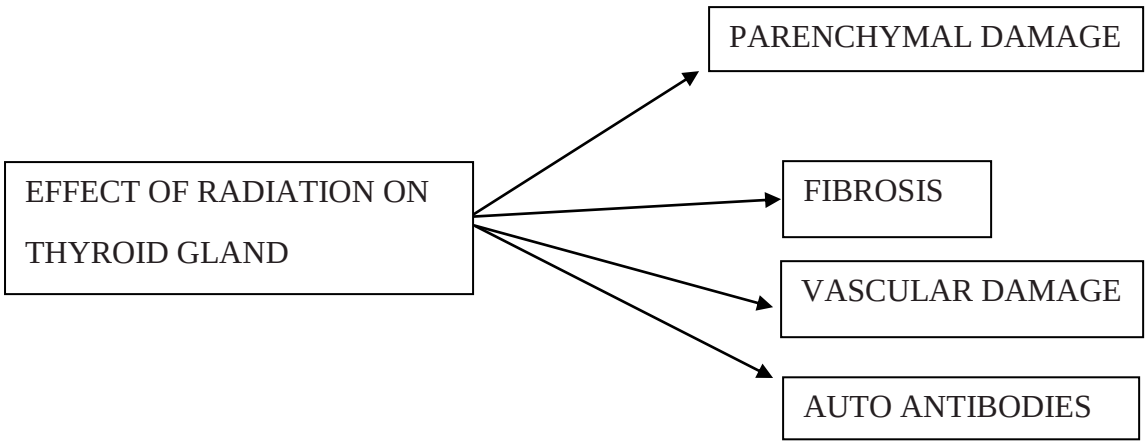
Radiation to the neck can affect the thyroid gland. The effect of radiation on thyroid gland reported in the literature are[38]

1) Primary hypothyroidism
2) Central hypothyroidism
3) Thyroiditis
4) Graves disease
5) Benign adenomas
6) Multinodular goiter
7) Radiation induced thyroid malignancies

The mean dose to the thyroid and the thyroid volume receiving more than a certain threshold dose are the important parameters for predicting RIHT (Radiation Induced Hypothyroidism) risk.[38,39,40]The incidence of hypothyroidism is less if the mean volume of thyroid gland is more than 8cc before radiation and if 3cc of thyroid gland is spared from the radiation.[40] Multiple factors are responsible for the incidence of RIHT, they are location of the radiation fields and the diagnostic intensity and sensitivity. Its been noted in a study that, the important criteria for radiotherapy to cause hypothyroidism were total dose of radiation and fractionation.[38,39] It has been observed that radiotherapy delivered to the thyroid region at doses of 45 Gy or higher resulted in biochemical evidence of primary hypothyroidism in at least 50% of the patients.[41]

The reported range of RIHT is 20% to 30% in patients receiving RT that include the neck. The majority (50%) of hypothyroidism occurs in first five years of follow up.[41] It has been documented that there is a relationship between dose and radiation induced hypothyroidism, but it is not well established. The incidence of hypothyroidism is more in females compared to males in general population, this risk is also observed in case of RIHT.[41] Age doesn't have any influence on the RIHT in the published studies. This is aganist other toxicities for example radiation-induced pneumonitis, where age has been shown to be a significant risk factor.[41] A partial thyroidectomy and the surgery which doesn't involve the thyroid gland however have a increased risk of RIHT, due to increased vascular damage when the two modalities are combined.[32,33]

Although several studies have examined risk of hypothyroidism in patients treated for nonthyroid head and neck cancers, incidence in these samples varied widely, ranging from 8% to 67%.[2,3,4,5,6,7] In addition, follow-up in the majority of these studies was limited, and thus it is uncertain how the magnitude of risk for developing hypothyroidism may change over time.



In patients with head and neck cancer, hypothyroidism is a toxicity associated with radiation treatment (RT) to lower neck fields that include the thyroid gland. Evidence suggests that radiation-induced parenchymal cell injury, fibrosis, vessel damage, and immune-mediated responses may contribute to impairment of thyroid function.[34]

Parenchymal damage: the thyrocytes are arranged in a follicle. These follicle may get disrupted after radiation. Radiation is also proven to inhibit the follicular epithelial function which can cause reduce thyroid hormone secretion.[34]

Fibrosis: the capsule of thyroid gland sends septae into the gland, these septae carry blood supply into the follicle, radiation not only affects supplying vessels but also causes fibrosis of the capsule.

Fibrosis of the capsule and septae inhibit compensatory hypertrophy and may lead to hypothyroidism.[42,43]

Vascular damage: A study by Feels has shown that radiation accelerates atherosclerosis of the carotid artery this could theoretically reduce the flow in superior thyroid artery and further lead to hypothyroidism.[44] when open wounds are exposed to radiation it is known to decrease capillary and fibroblast proliferation.[45] Radiation is known to cause acute injury to the endothelium of the capillaries. Rubin and Cassarett postulated that injury to thyroid vasculature occurred in biphasic mode.[46] In the initial phase there is injury to the endothelium which swells up and blocks the capillaries. In the late phase there is secondary degeneration of follicles due to progressive fibrosis of vessels.[47,48]

Autoantibodies: studies by Flatman had postulated that hypothyroidism following radiation may be due to an autoimmune response.[49]

Brachytherapy I 131 is proven to cause damage to thyrocytes and small thyroid vessels and also increases atherosclerosis of large vessels.[34]

Hypothalamus and pituitary gland is exposed to radiation in cases of nasopharyngeal, paranasal and certain brain tumours. Hypothalamus is more sensitive to radiation compared to pituitary gland. This may lead to hypopituitarism in the post radiation period.[50,51,52,53,54]

Samototrophs are most sensitive in the pituitary gland to radiation. Hence the most common hormone affected in hypopituitarism is growth hormone followed by ACTH and TSH.[50] The hypopituitarism patients might have either single or multiple hormone deficiency.The incidence of hypopuitarism depends on the dosage of

radiotherapy, the time since the patient has received the radiation and the chemotherapy. The two types of hypopituitarism is seen

1) Clinical hypopituitarism
2) Subclinical hypopuitarism

The frequency of hypothyroidism following treatment of head and neck cancer is more in laryngeal cancer. In a study radiotherapy with curative intent was given to ninety five early laryngeal cancer patients. The mean age of the patients was 66.1 years and the majority of patients were males with glottis as a common subsite. The incidence of hypothyroidism with a average follow up of 40 months is 46.9%. the majority of patients had developed hypothyroidism at 12 months.[55]

In a retrospective study of 504 patients with different Head and Neck cancers, radiotherapy was given as both definitive and adjuvant treatment with the mean age of 62 years. The longest period of followup in this study was 13.4 years. The incidence of hypothyroidism was 22% at 5 years and 49% at 10 years.[56]

Its been observed in the literature that by sparing the certain amount of thyroid volume (>3cc) the incidence of hypothyroidism may become less, hence IMRT can be used to spare the gland and concentrate the radiation to the tumour bed and in the region of recurrence. There is no study in the literature comparing the incidence of conventional radiotherapy with IMRT.[40]

EFFECT OF CHEMOTHERAPY ON THYROID GLAND

Addition of chemotherapeutic agents to conventional treatment has improved the outcome and survival in patients suffering from head and neck cancer. There is a varied opinion on the effect of chemotherapy on the thyroid gland. With only limited studies on the primary effect of chemotherapy on thyroid gland. Several studies which have studied the independent effect of chemotherapy on thyroid gland have shown no significant association between the two. Chemotherapy becomes the risk factor to develop hypothyroidism in patients receiving concomitant radiotherapy.[57] Endocrine disorders are one of the long term complication in patients treated for childhood malignancies.[58] Thyroid dysfunction is one among them. The incidence of hypothyroidism in children treated with chemotherapy is more compared to adults.[59] Targeted therapies and immunotherapies have recently been associated with thyroid dysfunction in contrast to other antineoplastic agents. Multiple drug regimens have been associated with increased frequency of hypothyroidism.

Only a small group of patients on cytotoxic agents such as cisplatin, 5 FU have developed hypothyroidism. Invitro studies have shown cisplatin in high doses to inhibit human throcytes, but clinical reports are not available except for transient decrease in thyroxine levels in patients receiving cisplatin. Variation in thyroglobulin level have been documented in patients receiving 5 FU but correlation with clinical manifestation is not available.[60,61,62,63,64] All the cytotoxic agents have shown to sensitize the thyroid gland to the effect of radiotherapy and thereby lead to hypothyroidism.[57]

In a randomized clinical study of ninety one patients diagnosed with oesophageal cancer and treated with concurrent chemoradiation (cisplatin and 5 FU + EBRT) . 15.5% of patient developed hypothyroidism after a follow up of five years.[65]

In a study involving thirty five patients with locally advanced squamous cell carcinoma of Head and Neck cancer were treated with concurrent chemoradiation (paclitaxel + radiation). After a median followup of 56.5 months 43% of patients developed hypothyroidism.[66]

Interferon alpha used in the treatment of melanoma is associated with development of destructive thyroiditis and autoimmune hypothyroidism.[67,68] Thalidomide and lenalidomide belongs to the immunomodulatory drug group with antineoplastic activity. Studies have shown that these drugs can cause hypothyroidism. Thalidomide and lenalidomide inhibits thyroid hormone secretion and iodine uptake into the follicular cells of thyroid gland.[69,70,71] Ipilimumab a anti-CTLA4 antibody is used in the treatment of unresectable or metastatic melanoma. In literature it is been shown that it can cause hypothyroidism.[72,73]

Tyrosine kinase inhibitors are the sepicific agents used in the treatment of several cancers. Inspite of its specific action it causes thyroid, gonadal and adrenal dysfunction.[74] In head and neck cancer treatment, the use of tyrosine kinase inhibitors are still under the clinical trial. Majority of tyrosine kinase inhibitors cause thyroid dysfunction except a few namely gefitinib and erlotinib. Tyrosine kinase inhibitors cause primary hypothyroidism. The mechanism of thyroid dysfunction is not clear.

The mechanisms that might cause thyroid dysfunction are[75,76]

1) Direct toxic effect on thyrocytes,
2) Impaired iodine uptake
3) Reduced synthesis of thyroid hormone due to inhibition of thyroid peroxidase enzyme.

In a non randomized prospective study of 35 patients of various head and neck cancer, breast cancer and lymphoma treated with EBRT and chemotherapy, 17% of patients developed hypothyroidism after a follow up of two years.[77]

Materials & Methods

MATERIALS AND METHODS

This prospective observational study was conducted from December 2013 to July 2015 in the department of Otorhinolaryngology Head and Neck surgery of R. L. Jalappa Hospital and Research Centre, Tamaka.

The study was approved by the Institutional ethical committee.

Written informed consent was taken from all patients included in the study.

METHOD OF COLLECTION OF DATA

The study group consisted of ninety patients treated for various Head and Neck cancers in the department of Otorhinolaryngology Head and Neck surgery of R. L. Jalappa Hospital and Research Centre, Tamaka.

INCLUSION CRITERIA

Patients diagnosed with Head and Neck cancer, treated by surgery, chemotherapy or radiotherapy in combination or as a single modality.

EXCLUSION CRITERIA

1) Patients with previous history of hypothyroidism
2) Patients who had total thyroidectomy
3) Patients with familial history of thyroid disorders

TREATMENT:

The patients included in the study underwent either surgery, radiotherapy or chemotherapy as a single modality or as a combined modality of treatment.

Surgery: Patients treated by surgery underwent excision of the primary tumour and suitable type of neck dissection when indicated and reconstructed using regional flaps

Radiotherapy: Cobalt-60 machine was used to administer radiotherapy. In definitive radiotherapy the dose of radiation given to tumour bed and neck was 66Gy and in case of adjuvant settings the radiation given to tumour bed and neck was 60Gy. Patients received radiotherapy in a dose of 1.8-2.0 Gy/dose for 5 days in a week for 6-7 week.

The radiation field in case of laryngeal, hypopharyngeal and oropharyngeal cancers includes the both neck field with the midline. In case of oral cavity carcinoma, the radiation field includes the tumour bed and the ipsilateral side of the neck not crossing the midline.

Chemotherapy: cisplatin 100mg/m2 and 5 FU 1000/m2 were the drugs used in the patients included in the study either in neoadjuvant setting or concurrent setting.

A thorough clinical history was obtained and examination performed with special emphasis on clinical symptoms and signs of hypothyroidism. Thyroid hormone profile that included , T_3 (tri-iodo thyronine, T_4 (tetra-iodo thyronine) and TSH (Thyroid Stimulating Hormone) was obtained pretreatment, three months, six months post treatment and one year when ever possible.

METHOD OF THYROID FUNCTION TEST:

Thyroid function test of all the patients included in the study was done in the Central Biochemistry Laboratory R L Jalappa Hospital ,Tamaka, Kolar.

2-2.5 ml of venous blood was collected from the patient (fasting sample). Serum was separated after centrifugation and thyroid hormone levels T3 (tri-iodo thyronine), T4(tetra-iodo thyronine) and TSH (Thyroid Stimulating Hormone) was estimated using

ELECTRO CHEMILUMINESCENT IMMUNO ASSAY method

Normal values

T_3 (tri-iodo thyronine) -	adults <60 years	:	0.7-2.0ng/ml
	>60 years	:	0.4-1.8ng/ml
T_4 (tetra-iodo thyronine) -	adults <60 years	:	4.5-11.0mcg/dl
	>60 years	:	5.0-11.7mcg/dl
TSH(Thyroid Stimulating Hormone) -adults < 60 years:			0.4-4.2 mcIu/ml
	>60 years	:	0.5- 8.9mcIu/ml

Subclinical and Overt hypothyroidism:

Patient is considered subclinically hypothyroid if TSH(Thyroid Stimulating Hormone) levels in adults was morethan 4.2 mcIu/ml and in patients above sixty years morethan 8.9 mcIU/ml with normal T_3 (tri-iodo thyronine), T_4 (tetra-iodo thyronine) levels.

Overt hypothyroid if TSH (Thyroid Stimulating Hormone) levels in adults was morethan 4.2 mcIu/ml, T_3 (triiodo thyronine) levels less than 0.7ng/ml and T_4

(tetraiodo thyronine) less than 4.5mcg/dl and in patients above sixty years TSH (Thyroid Stimulating Hormone) levels morethan 8.9 mcIU/ml, T_3 (tri-iodo thyronine) levels lessthan0.4ng/ml and,

T_4 (tetra-iodo thyronine) levels less than 5.0 mcg/dl.

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Chi-square/ Fisher Exact test was used as tests of significance. Continuous data was represented as mean and standard deviation. Wilcoxon signed rank test is the test of significance for paired data such as before and after treatment (TSH level comparisons) p value <0.05 was considered as statistically significant.

Results

OBSERVATIONS AND RESULTS:

Our study included totally ninety patients, with squamous cell carcinoma of Head and Neck region. Ninety patients were followed up for six months and fifty eight patients are followed up for one year.

Table 2: Age distribution of patients included in the study (n=90)

Age	Frequency (n=90)	Percent
< 40 years	11	12.2
41 to 50 years	27	30.0
51 to 60 years	29	32.2
> 60 years	23	25.6
Mean Age	54.05 ± 10.106	

Majority of patients were in the age group 51 to 60 years (32.2%)

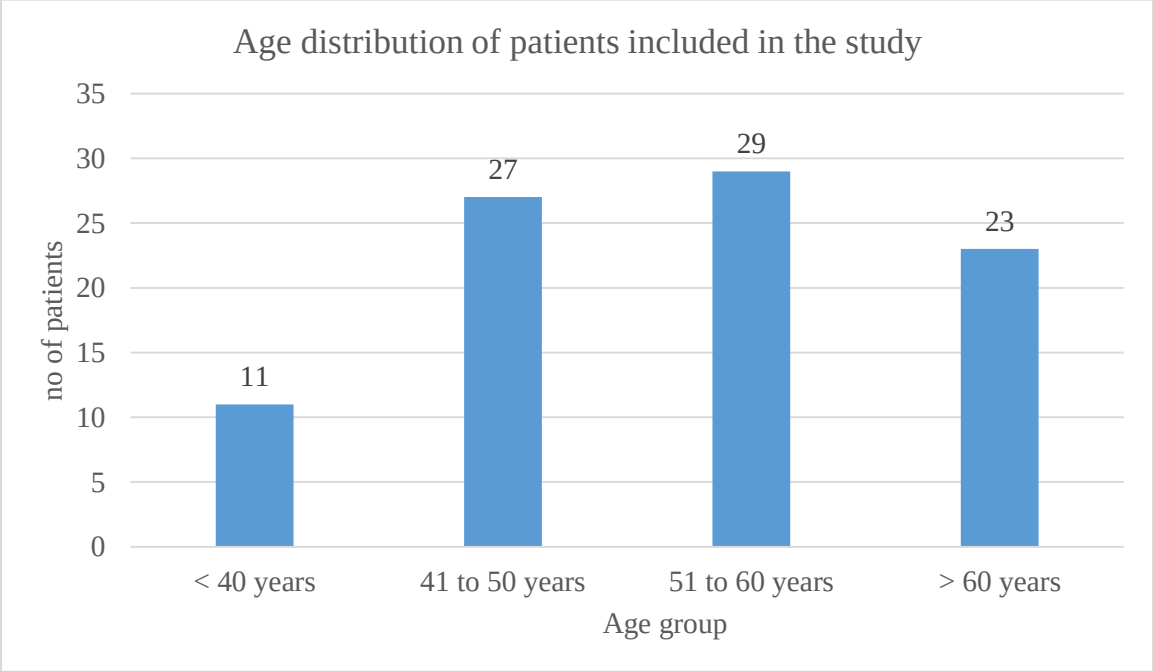


Figure 6 :Bar diagram depicting age distribution of patients included in the study

Table 3: Sex distribution of patients included in the study

Sex	Frequency	Percent
Female	43	47.8
Male	47	52.2
Total	90	100.0

52.2% of patients were males and 47.8% were females.

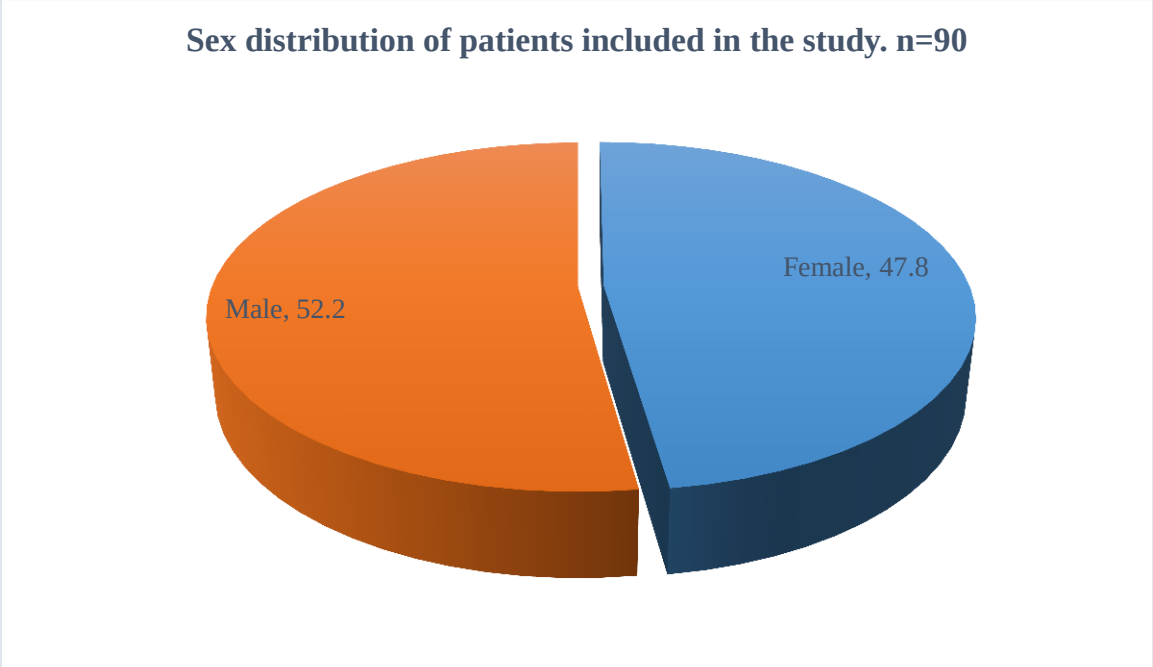


Figure 7 : Pie diagram showing Sex Distribution

Table 4: Site of primary tumour in the patients included in the study

Site of primary tumour in the patients n=90	Frequency	Percent
Carcinoma Oral Cavity	63	70.0
Carcinoma Oropharynx	12	13.3
Carcinoma Larynx	10	11.1
Carcinoma Hypopharynx	5	5.6

Our study had highest patients with primary tumour in oral cavity

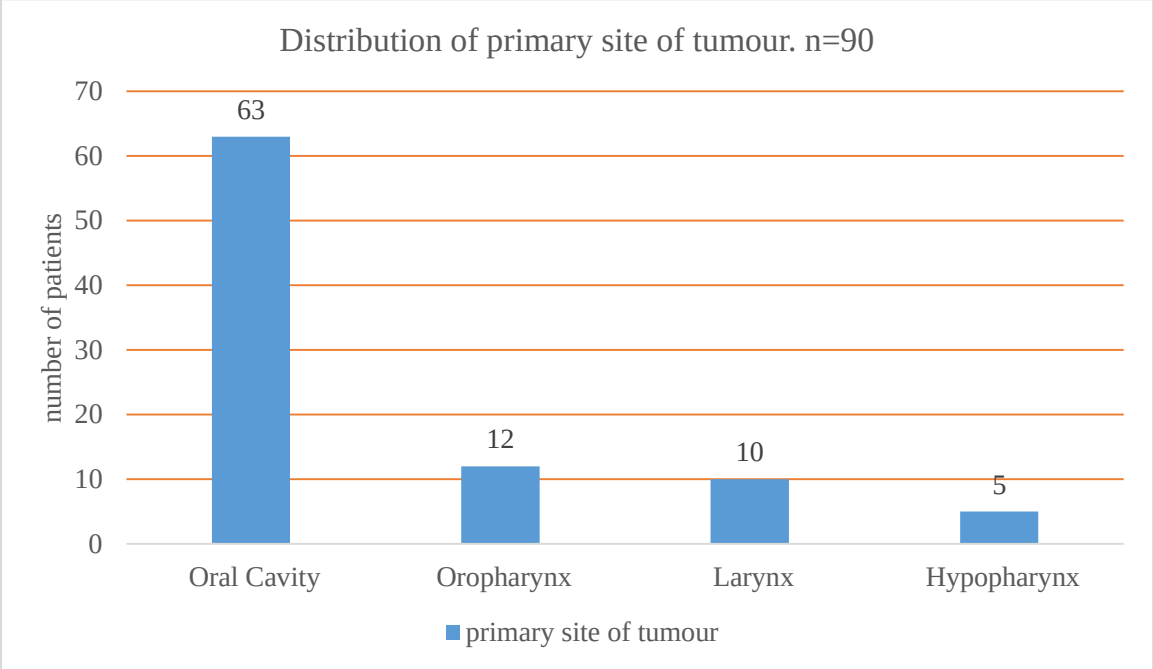


Figure 8: Bar diagram depicting distribution of primary site of tumour in Head and Neck cancer patients

Table 5: T staging of Tumors according to AJCC classification in the study

T Staging	Frequency n=90	Percent
T1	1	1.1
T2	12	13.3
T3	31	34.4
T4a	44	48.8
T4b	2	2.2

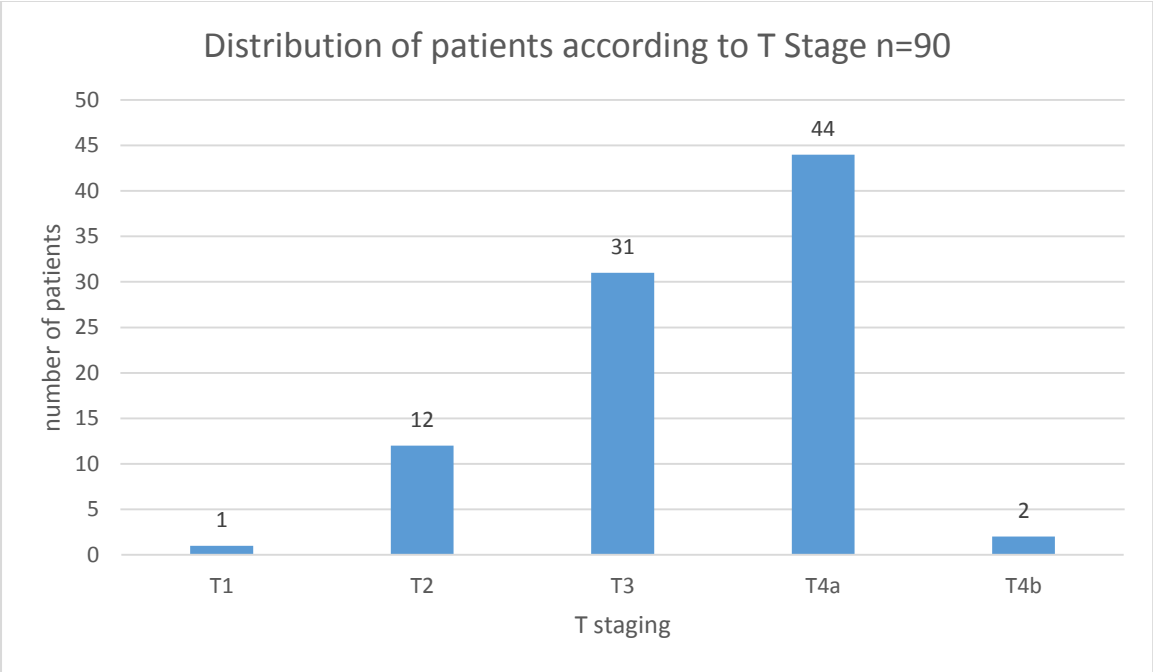


Fig 9 : Bar diagram showing distribution of T stage according to AJCC classification in the patients included in the study

Table 6: N Staging of patients included in the patients

N Stage	Number of patients (n=90)	Percentage
N0	19	21.1
N1	46	51.1
N2a	10	11.1
N2b	11	12.2
N2c	3	3.3
N3	1	1.1

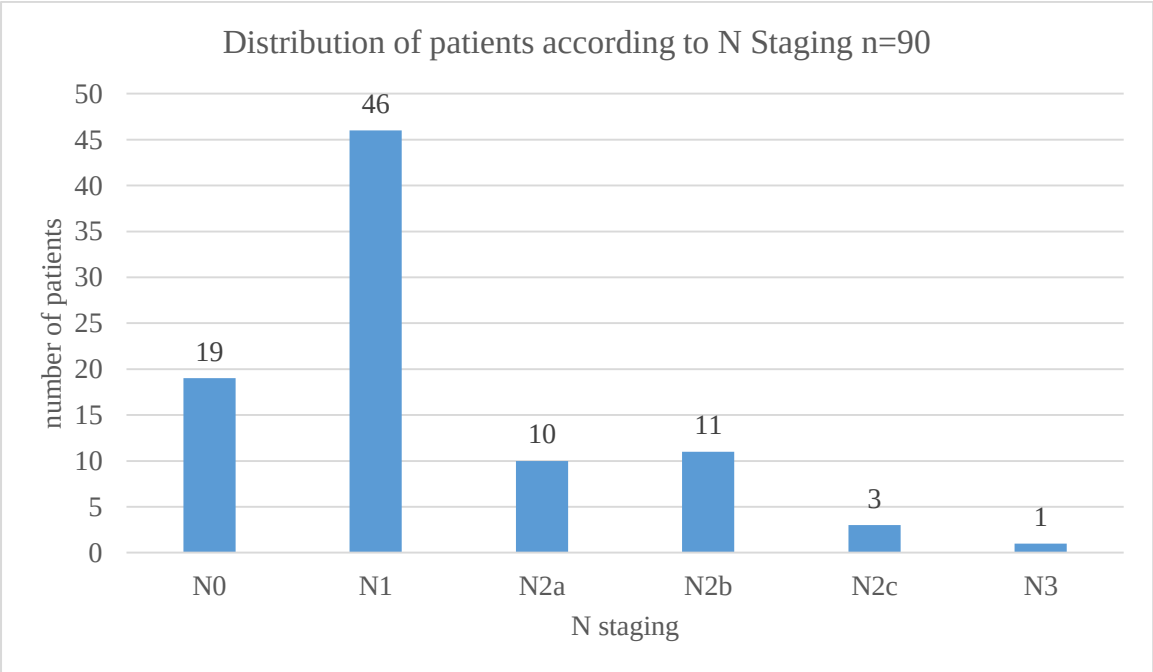


Figure 10: Bar diagram showing Nodal stages in TNM staging according to AJCC classification

Table 7: Stage of Tumor in the Head and Neck cancer patients according to AJCC TNM classification 2012

Stage	Frequency	Percent
I	1	1.1
II	2	2.2
III	29	32.2
IV	58	64.4

64.4% of patients were in stage 4, 32.2% were in stage 3.

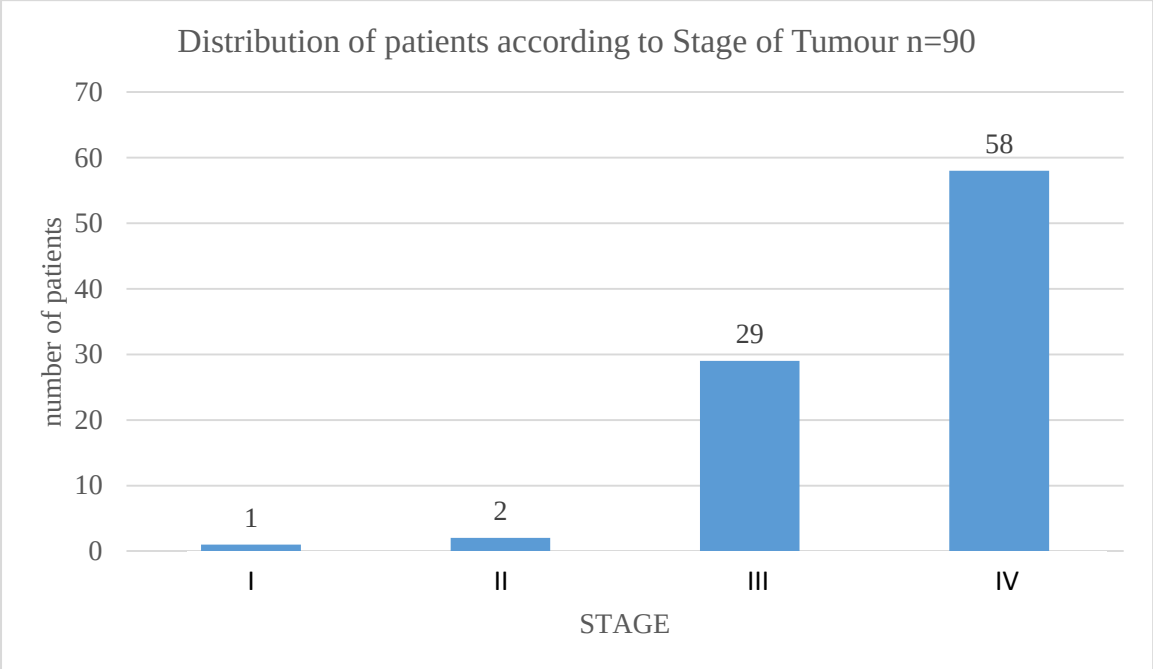


Figure 11: Bar diagram showing Stage of Tumor according to AJCC TNM classification

Table 8: Distribution of Head and Neck cancer patients according to Treatment modality

Treatment	Frequency n=90	Percent
Surgery + RT	51	56.7
RT + CT	22	24.4
Surgery + RT + CT	11	12.2
Only Surgery	5	5.6
Only RT	1	1.1

56.7% of patients were treated by Surgery + RT, 24.4% by CT+RT & 12.2% by Surgery + CT+RT.

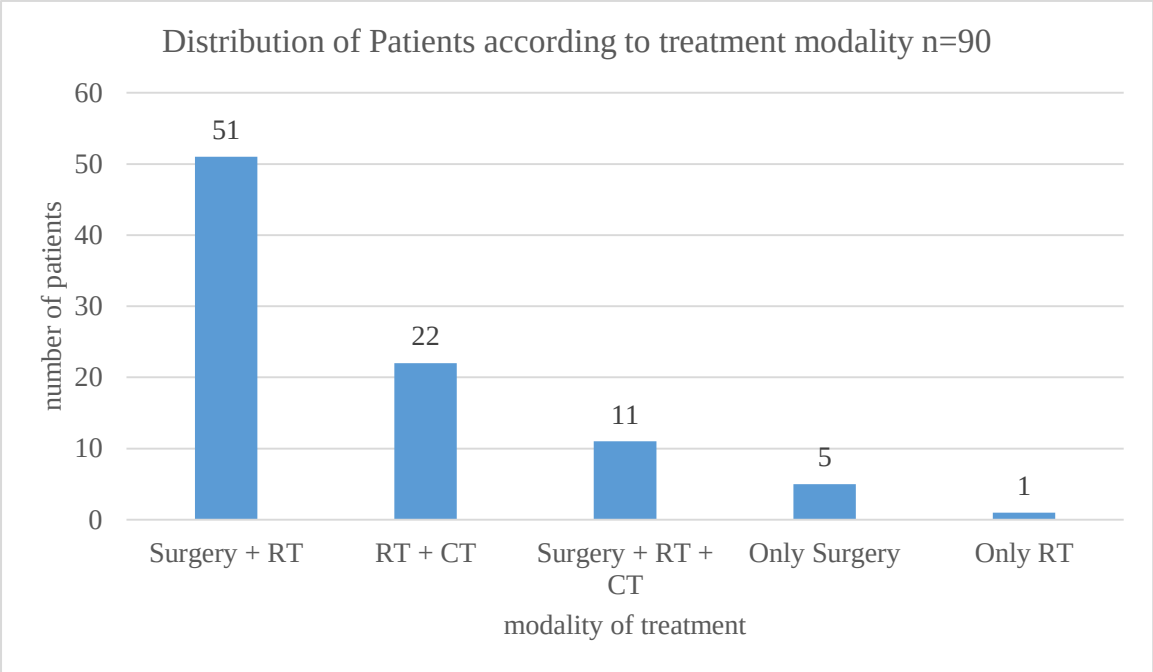


Figure 12: Bar diagram showing distribution of patients according to Treatment modality

Table 9: Thyroid Profile of patients at Baseline, 3 months, 6 months and 1 year

	Euthyroid		Hypothyroid	
	Count	%	Count	%
Baseline (n=90)	90	100	-	
TSH 3 month (n= 90)	87	97%	3	3%
TSH 6 month (n = 90)	83	92%	7	8%
TSH 1 year (n=58)	49	84%	9	16%

At baseline all the subjects were Euthyroid, at 3 months 3% developed hypothyroidism, at 6 months 8% developed hypothyroidism and at 1 year 16% developed hypothyroidism.

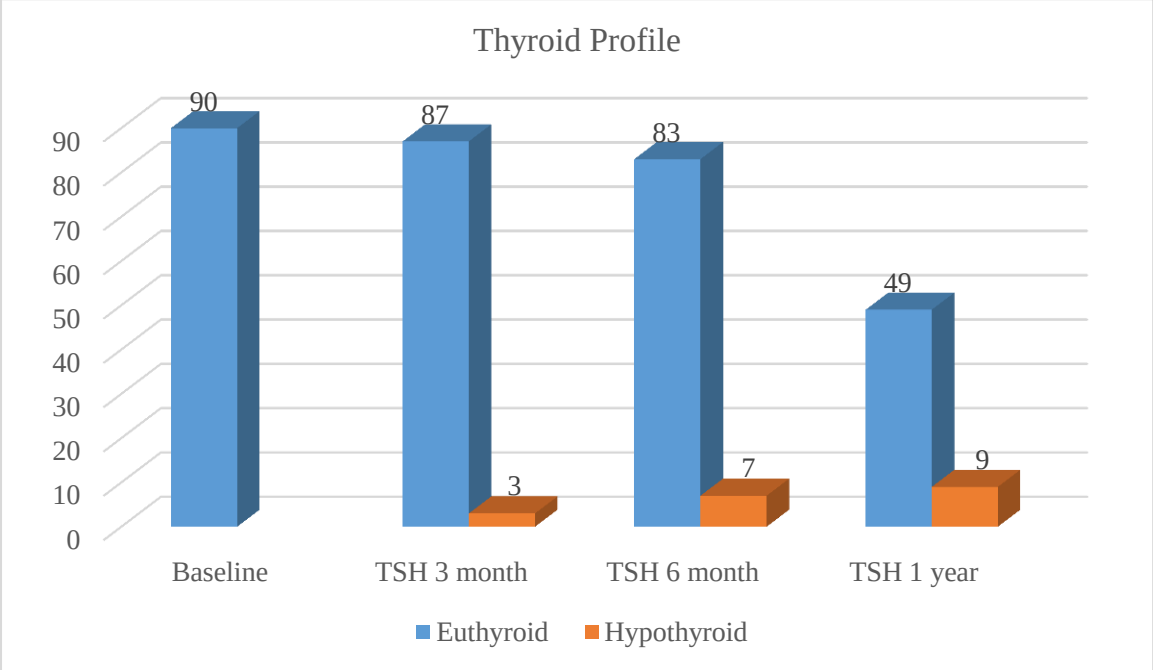


Figure 13: Bar diagram showing Thyroid Profile of patients at baseline, 3 months, 6 months and 1 year.

Table 10: TSH values Descriptive Statistics and Comparison of TSH values at 3 months, 6 months and 1 year with baseline TSH

Descriptive Statistics								
	N	Mean	Std. Deviation	Minimum	Maximum	Percentiles		
						25th	Median	75th
TSH Baseline	90	3.07	0.92	0.47	4.13	2.69	3.30	3.86
TSH at 3 month	90	4.26	7.99	0.47	73.60	2.77	3.25	4.00
TSH at 6 month	90	4.08	4.73	0.46	36.00	2.90	3.45	3.90
TSH at 1 year	58	4.02	5.01	0.80	36.30	2.92	3.47	4.00

Ranks				
		N	Mean Rank	Sum of Ranks
TSH at 3 months – TSH Baseline	Negative Ranks	36	39.32	1415.50
	Positive Ranks	54	49.62	2679.50
	Ties	0		
	Total	90		
TSH at 6 months – TSH Baseline	Negative Ranks	31	31.44	974.50
	Positive Ranks	51	47.62	2428.50
	Ties	4		
	Total	90		
TSH 1 year – TSH Baseline	Negative Ranks	11	15.82	174.00
	Positive Ranks	35	25.91	907.00
	Ties	2		
	Total	58		

Test Statistics[a]			
	TSH at 3 mon – TSH Baseline	TSH at 6 mon – TSH Baseline	TSH1year – TSH Baseline
Z	-2.545[b]	-3.362[b]	-4.004[b]
P value	0.011*	0.001*	<0.0001*
a. Wilcoxon Signed Ranks Test			
b. Based on positive ranks.			

As the distribution of TSH values not following Normal distribution, Wilcoxon signed rank test was performed to find the difference in TSH levels at 3 months, 6 months and at 1 year from baseline.

A Wilcoxon signed-rank test showed that statistically significant change in TSH values at 3 months, 6 months and 1 year follow-up when compared to baseline TSH.

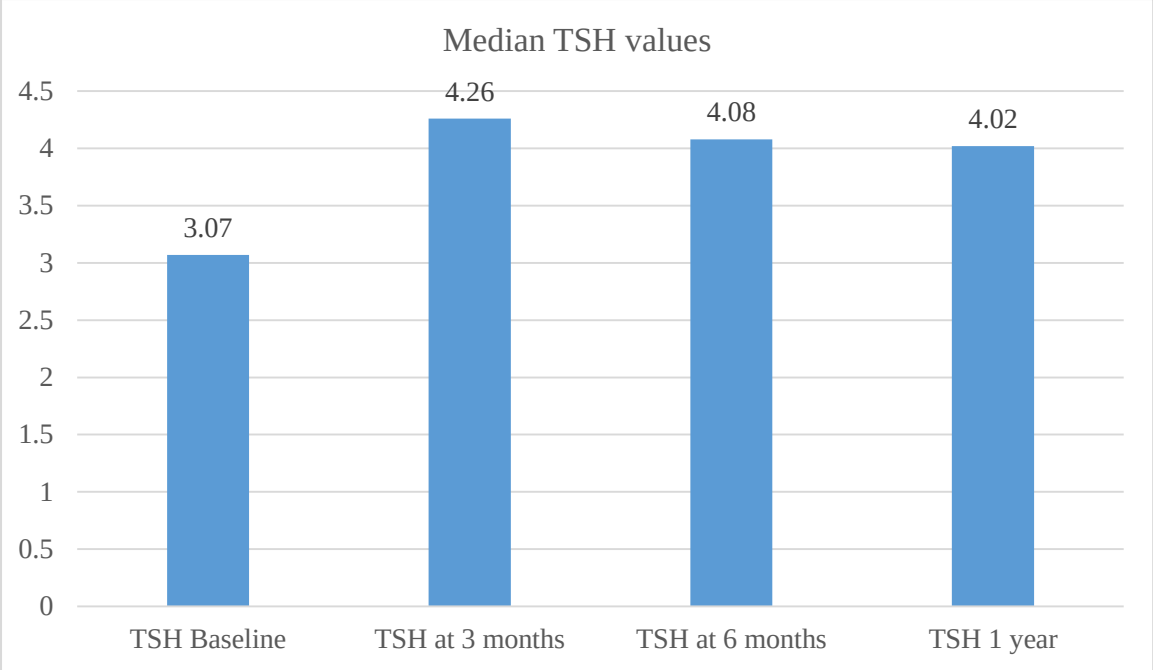


Figure 14: Bar diagram showing Median TSH values at baseline, 3 months, 6 months and 1 year.

Table 11 : T3 values Descriptive Statistics and Comparison of TSH values at 3 months, 6 months and 1 year with baseline TSH

Descriptive Statistics								
	N	Mean	SD	Minimum	Maximum	Percentiles		
						25th	Median	75th
T3 baseline	90	1.3511	1.263	0.80	13.00	1.0000	1.2000	1.4000
T3 at 3month	90	1.3428	1.273	0.20	13.00	1.0000	1.3000	1.4000
T3 at 6month	87	1.2362	0.245	0.80	1.80	1.0000	1.3000	1.4000
T3 at 1yr	49	1.1592	0.248	0.70	1.60	.9000	1.2000	1.3000

Test Statistics[a]			
	T3 Baseline vs 3 month	T3 baseline vs T3 6 month	T3 baseline vs T3 1yr
Z	-0.201	-0.116	-1.450
P value	0.841	0.908	0.147
a. Wilcoxon Signed Ranks Test			
b. Based on positive ranks.			

There was no significant difference in T3 level at 3 month, 6 months and 1 year compared to baseline T3 value.

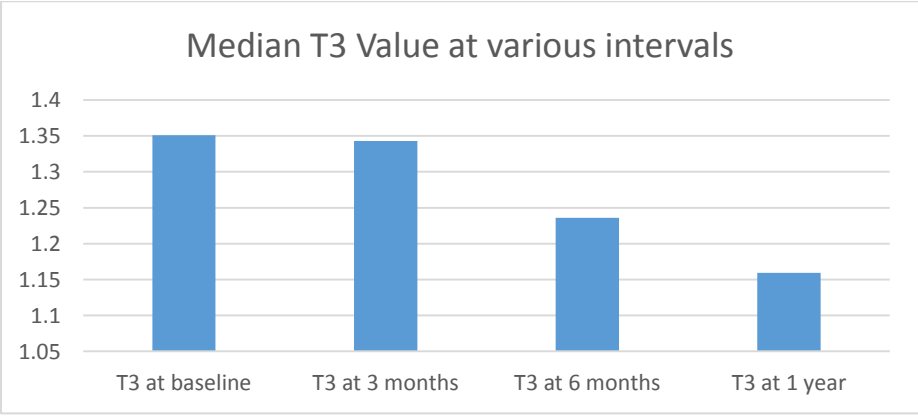


Figure 15 : Bar diagram showing median T3 at pretreatment, at 3 months, at 6 months and 1 year

Table 12 : T4 values Descriptive Statistics and Comparison of TSH values at 3 months, 6 months and 1 year with baseline TSH

Descriptive Statistics								
	N	Mean	SD	Minimum	Maximum	Percentiles		
						25th	Median	75th
T4 baseline	90	5.802	0.828	4.60	8.00	5.1000	5.7000	6.1000
T4 3month	90	5.761	0.861	3.90	8.00	5.1000	5.6000	6.1000
T4 6month	87	5.7901	0.808	4.60	8.00	5.2000	5.6000	6.1000
T4 1yr	49	5.8018	0.788	4.90	8.00	5.2000	5.5000	6.2500

Test Statistics[a]			
	T4 Baseline vs 3 month	T4 baseline vs T3 6 month	T4 baseline vs T3 1yr
Z	-0.377	-0.195	-2.000
P value	0.706	0.845	0.550
a. Wilcoxon Signed Ranks Test			
b. Based on positive ranks.			

There was no significant difference in T4 level at 3 month, 6 months and 1 year compared to baseline T4 value.

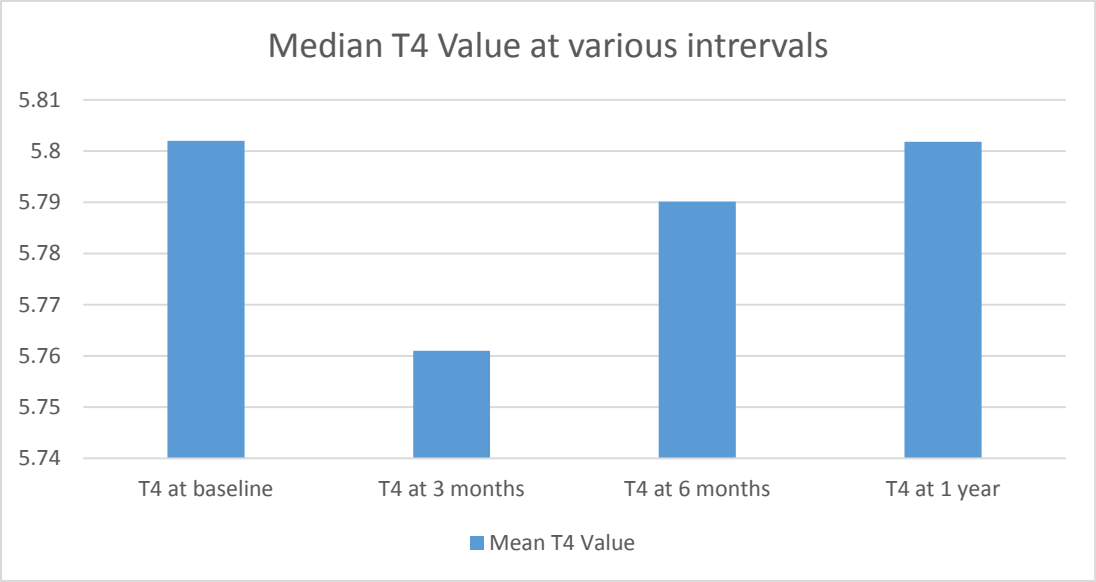


Figure 16 : bar diagram showing the median T4 at pretreatment, at 3 months, 6 months and 1 year

Table 13: SEX Distribution of patients who developed hypothyroidism

SEX	No of patients (n=9)
Male	6
Female	3

In our study three female patients and six male patients developed hypothyroidism

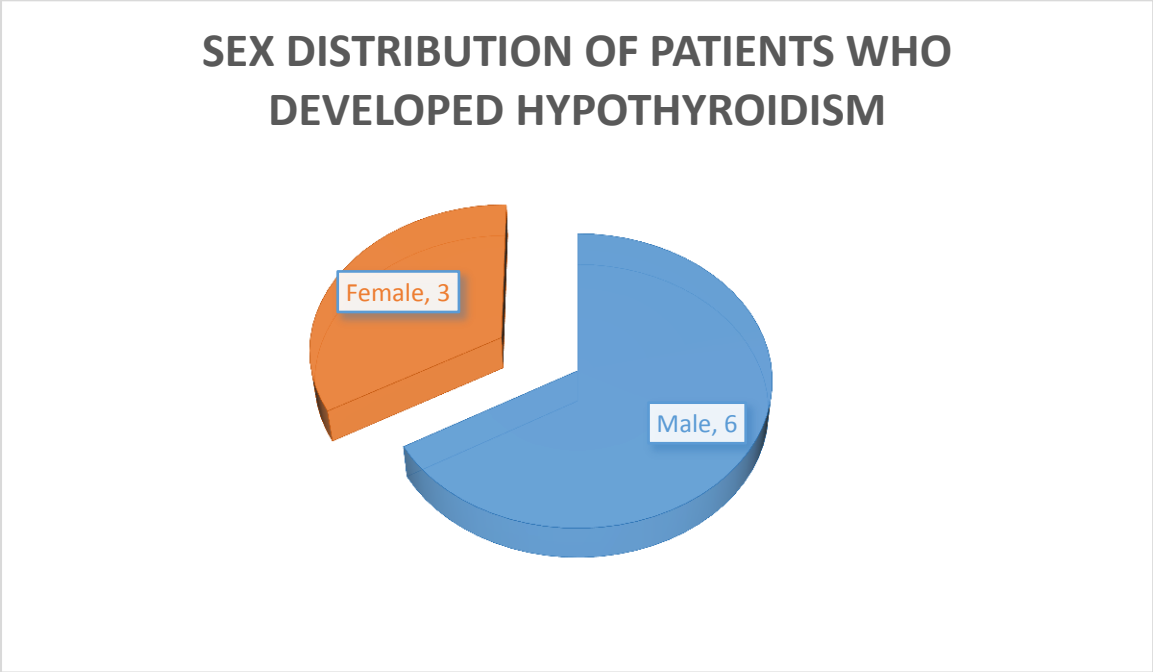


Figure 17: pie diagram showing sex distribution of patients who developed hypothyroidism

Table 14: Distribution of patients according to hypothyroid status

Hypothyroid status	Number of patients (n=9)
Subclinical hypothyroidism	7
Clinical hypothyroidism	2

In our study seven patients developed subclinical hypothyroidism and two patients developed clinical hypothyroidism

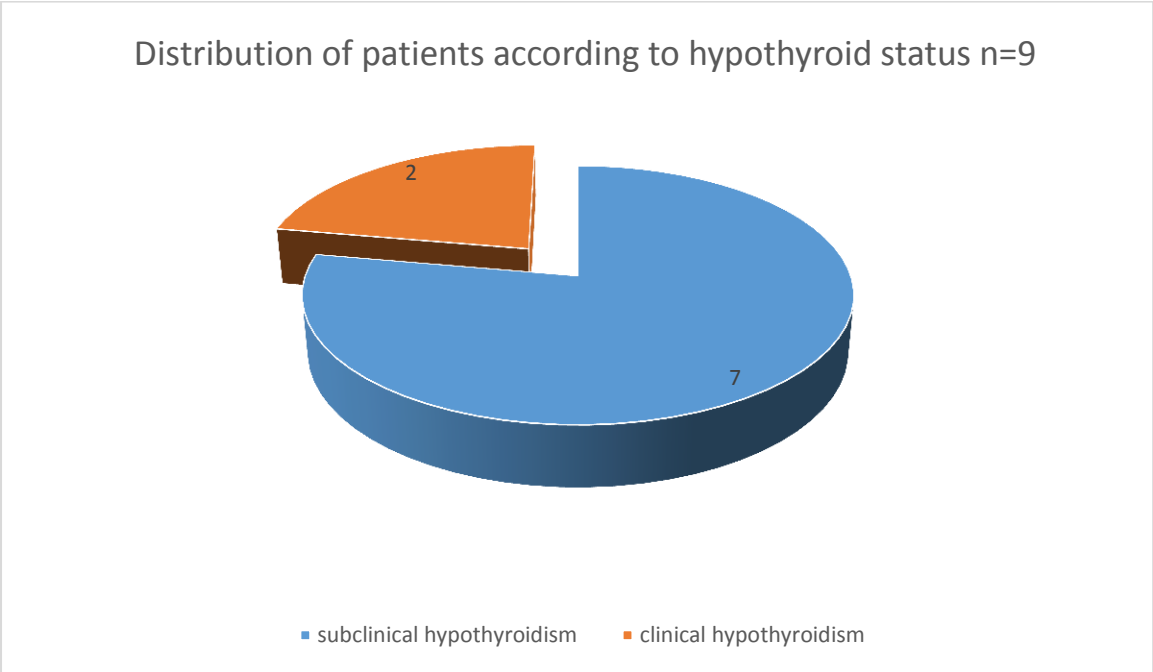


Figure 18: pie diagram showing distribution of patients according to hypothyroid status

Table 15: Association between Age and Hypothyroidism at various intervals

		Age				P value (Fischer's Exact Test)
		< 60 years		> 60 years		
		Count	%	Count	%	
at 3 month	Euthyroid	65	97.01%	22	95.65%	0.75
	Hypothyroid	2	2.99%	1	4.35%	
at 6 month	Euthyroid	63	94.03%	20	86.96%	0.27
	Hypothyroid	4	5.97%	3	13.04%	
at 1 year	Euthyroid	36	87.80%	13	76.47%	0.277
	Hypothyroid	5	12.20%	4	23.53%	

There was no significant association between Age and Hypothyroidism at 3 months, 6 months and 1 year.

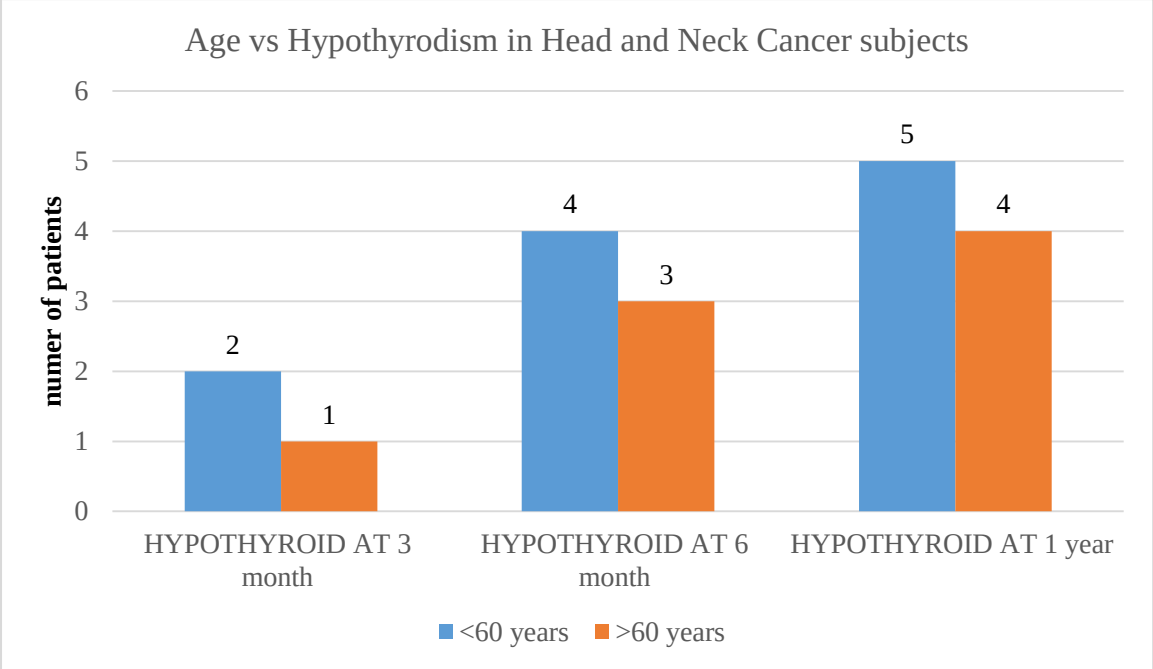


Figure 19: Bar diagram showing association between age and hypothyroidism

Table 16: Association between Treatment modality and Hypothyroidism in Head and Neck cancer patient

		Treatment										P value
		Surgery + RT		RT + CT		Surgery + RT + CT		Only Surgery		Only RT		
		Count	%	Count	%	Count	%	Count	%	Count	%	
at three months	Euthyroid	48	94.1%	22	100.0%	11	100.0%	5	100.0%	1	100.0%	0.667
	Hypothyroid	3	5.9%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	
at six months	Euthyroid	45	93.8%	21	95.5%	11	100.0%	5	100.0%	1	100.0%	0.891
	Hypothyroid	3	6.2%	1	4.5%	0	0.0%	0	0.0%	0	0.0%	
at one year	Euthyroid	28	96.6%	8	100.0%	6	85.7%	5	100.0%	0	0.0%	0.485
	Hypothyroid	1	3.4%	0	0.0%	1	14.3%	0	0.0%	0	0.0%	

In our study 51 patients underwent Surgery + RT at 3 months & 6 months 3 of them had hypothyroidism and 1 year 1 patient had hypothyroidism. There was no significant difference between treatment modality and incidence of hypothyroidism at all the intervals.

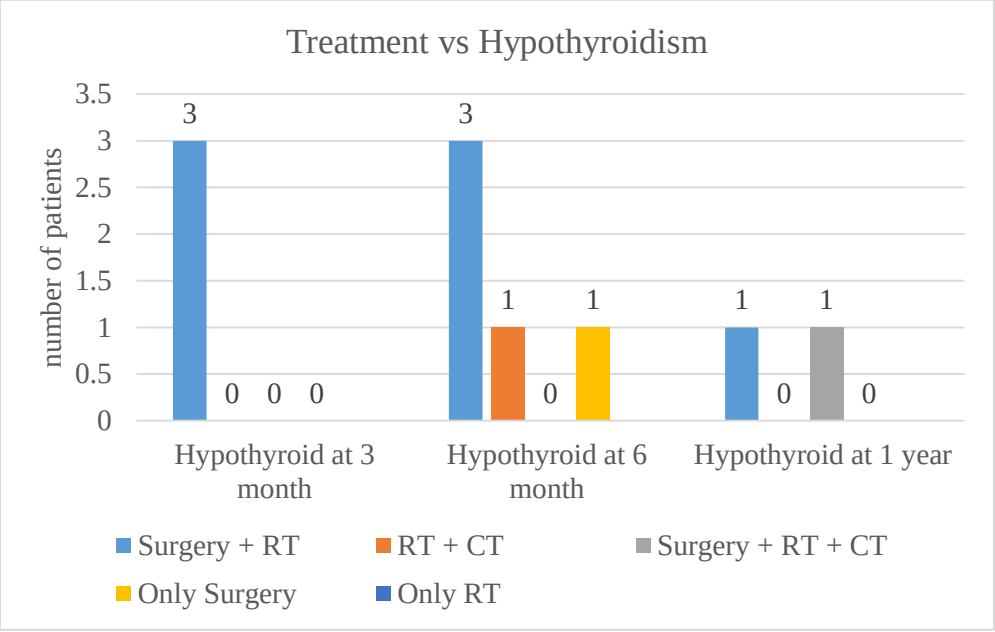


Figure 20: Bar diagram showing Association between Treatment modality and Hypothyroidism in Head and Neck cancer patients

Table 17: Number of patients who took radiotherapy as a single/multimodality treatment

	Number of patients
Adjuvant radiatiotherapy	62
Definitive radiotherapy	20
Palliative radiotherapy	3
total	85

In our study eighty five patients received radiotherapy

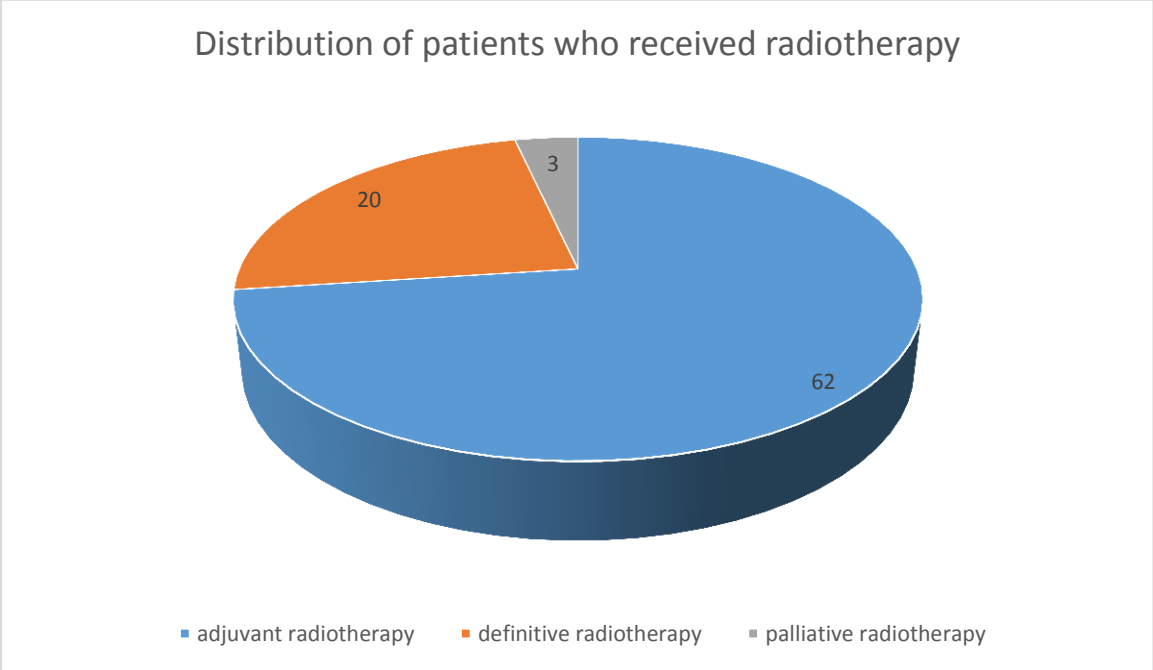


Figure 21: pie diagram showing distribution of patients who received radiotherapy

Table 18: Association between site of primary tumour and Hypothyroidism in Head and Neck cancer patients

	Site of primary tumour								P value
	Oral Cavity		Oropharynx		Larynx		Hypopharynx		
	Count	%	Count	%	Count	%	Count	%	
Euthyroid	62	98.4%	12	100.0%	9	90.0%	4	80.0%	0.082
Hypothyroid	1	1.6%	0	0.0%	1	10.0%	1	20.0%	
Euthyroid	61	98.4%	11	91.7%	7	77.8%	4	100.0%	0.042*
Hypothyroid	1	1.6%	1	8.3%	2	22.2%	0	0.0%	
Euthyroid	38	95.0%	3	100.0%	3	100.0%	3	100.0%	0.926
Hypothyroid	2	5.0%	0	0.0%	0	0.0%	0	0.0%	

At 3 months 1 case of hypothyroidism was seen in Oral cavity, Larynx and hypopharynx respectively. There was no significant association between hypothyroidism and site of primary at 3 months.

At 6 months 2 cases of hypothyroidism was seen in larynx, 1 case in oral cavity & oropharynx respectively. There was significant association between hypothyroidism and site of primary at 6 months

At 1 year 2 cases of hypothyroidism was seen in Oral cavity only. There was no significant association between hypothyroidism and site of primary at 1 year.

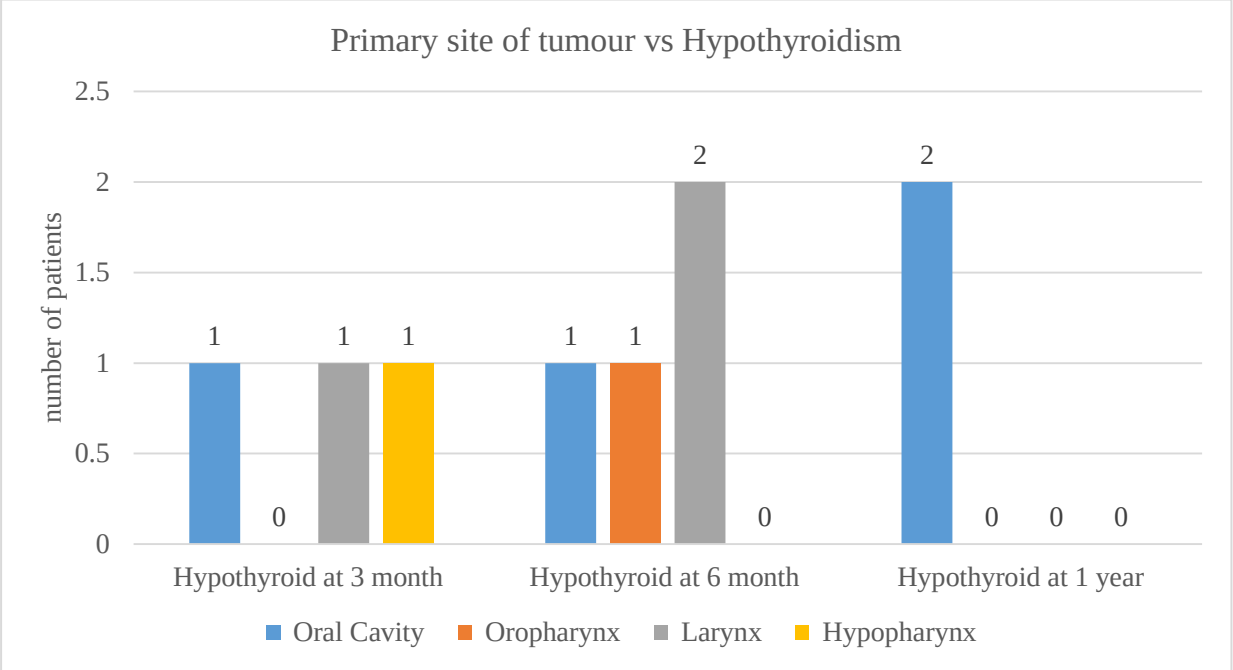


Figure 22: Bar diagram showing Association between Diagnosis and Hypothyroidism in Head and Neck cancer patients

Table 19: Association between Stage of Tumour and Hypothyroidism in Head and neck cancer patients

Stage	At 3 month				At 6 month				At 1 year			
	Euthyroid		Hypothyroid		Euthyroid		Hypothyroid		Euthyroid		Hypothyroid	
	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%
1	1	1.1%	0	0.0%	1	1.2%	0	0.0%	1	2.1%	0	0.0%
2	2	2.3%	0	0.0%	2	2.4%	0	0.0%	0	0.0%	0	0.0%
3	28	32.2%	1	33.3%	25	30.1%	3	75.0%	13	27.7%	2	100.0 %
4	56	64.4%	2	66.7%	55	66.3%	1	25.0%	33	70.2%	0	0.0%
P value	0.991				0.315				0.094			

** More than 20% of cells in this sub table have expected cell counts less than 5. Chi-square results may be invalid.*

There was no significant association between Stage of Tumor and Hypothyroidism at 3 month, 6 month & 1 year in the study. All the hypothyroid cases at 1 year were seen in stage 3 subjects.

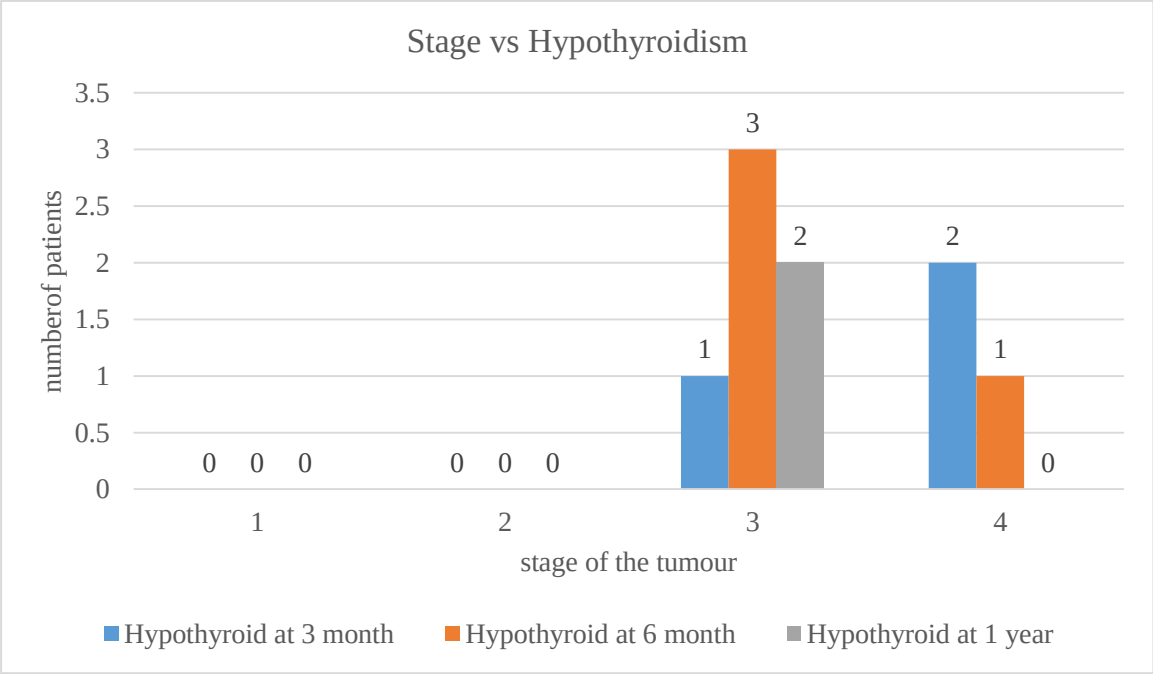


Figure 23: Bar diagram showing Association between Stage of Tumour and Hypothyroidism in Head and Neck cancer patients.

Figure 24: Photograph of chemiluminescence machine used for thyroid function tests

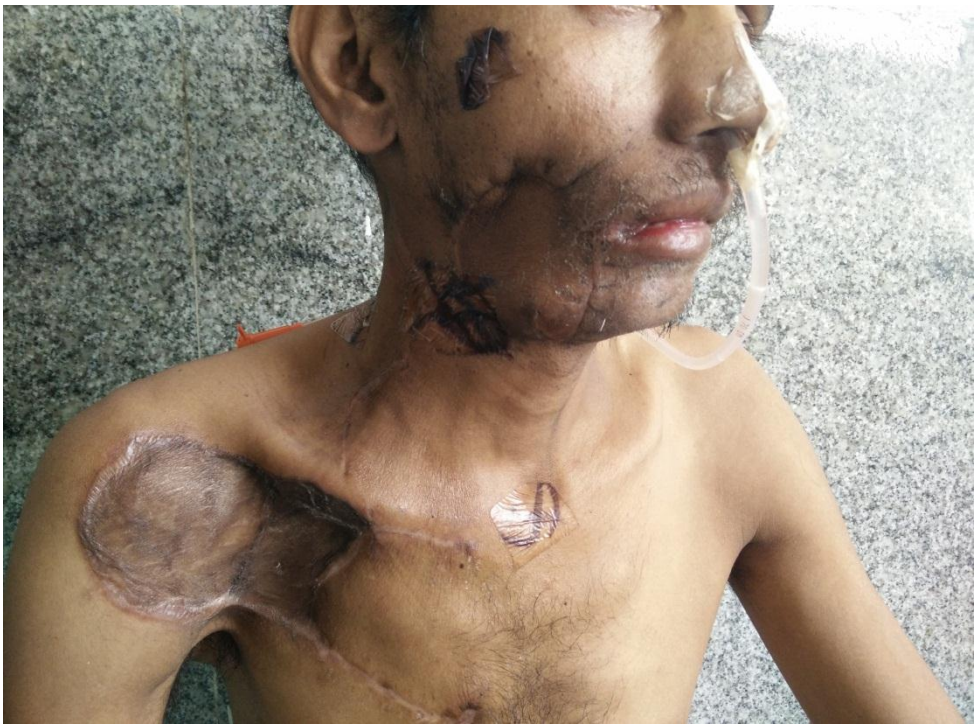


Figure 25: Photograph of radiation field in oral cavity carcinoma.

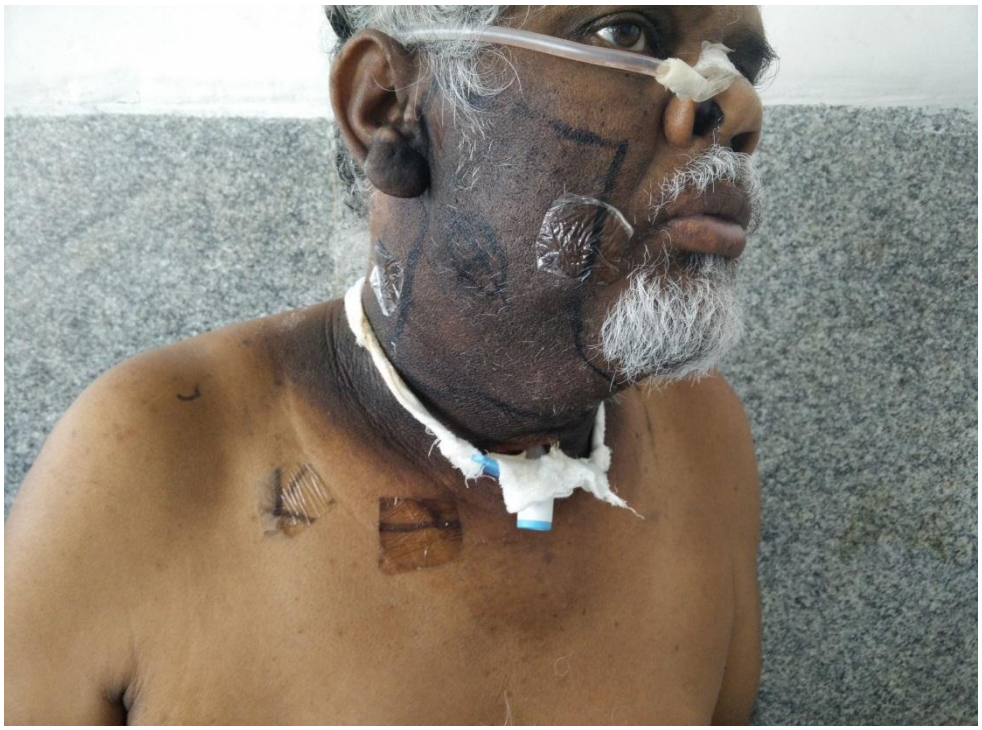


Figure 26: Photograph of patient who developed hypothyroidism in post treatment period (right)

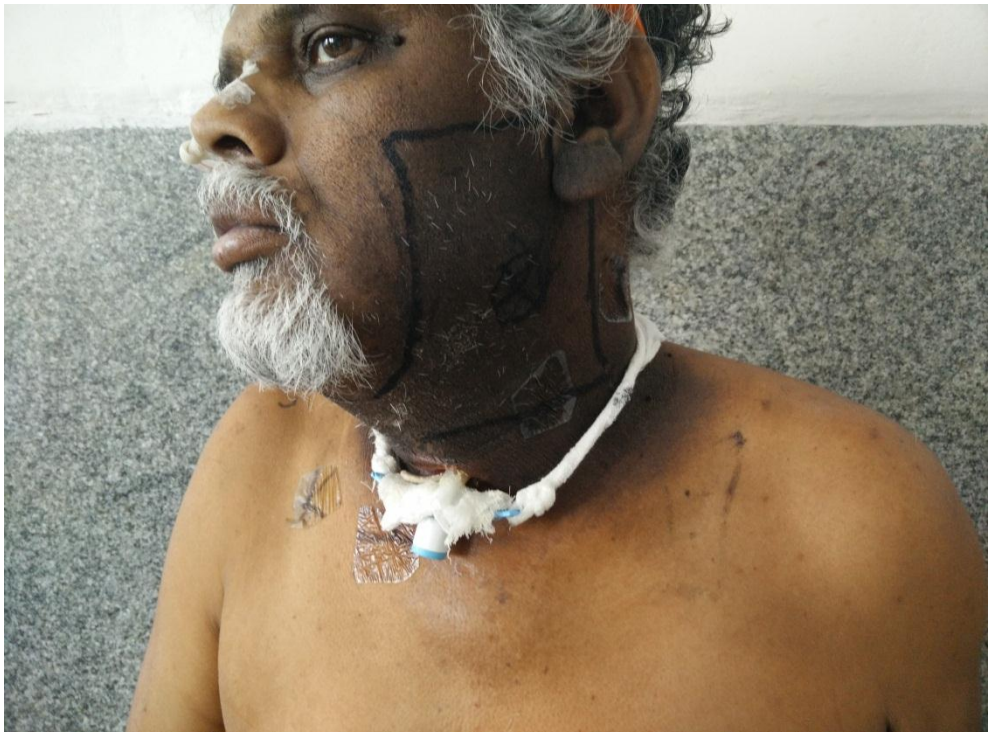


Figure 27: Photograph of radiation field in oropharyngeal carcinoma (Left)

Discussion

DISCUSSION

In India, majority of Head and Neck cancers (60-80%), present in advanced stage disease (stage 3 and stage 4).[1] Multimodality treatment that includes, surgery, chemotherapy and radiotherapy, in various combination forms the standard of care for these patients. The treatment for Head and Neck cancer by different modalities have morbidities, such as xerostomia, radiation fibrosis, ototoxicity, ocular toxicity, esophageal stricture, osteoradionecrosis and trismus, some of which are preventable and treatable once diagnosed. One such easily diagnosed and treatable morbidity following treatment for Head and Neck cancer is hypothyroidism, which is often overlooked. Diagnosis of post treatment hypothyroidism in a case of head and neck cancer can be challenging, if based only on symptoms or clinical examination, since the symptoms of hypothyroidism can be masked by the primary disease. The common manifestations of overt hypothyroidism are slowed mentation, depression, skin dryness, pleural and pericardial effusions, decreased gastrointestinal motility, weight gain and cold intolerance. The potential post treatment complications in patient who develop hypothyroidism are delayed wound healing, impaired development of tracheoesophageal speech, acceleration of atherosclerosis, hypercholesterolemia, pharyngocutaneous fistula and an increased chance of developing thyroid malignancies in the future. In literature there is paucity of studies about the onset and incidence of hypothyroidism following treatment of Head and Neck cancer.

The incidence of hypothyroidism from treatment of head and neck cancer varies from

8-67%.[2,3,4,5,6] There is a wide variation in the incidence of post treatment hypothyroidism in Head and Neck cancer patients. This difference is due to variation in the gender distribution, number of patients included in the study, various stages of the cancer at presentation, different modalities of treatment, different subsites of cancer like oral cavity, oropharynx, larynx and hypopharynx, follow-up period and availability of thyroid profile in retrospective studies. The incidence of hypothyroidism in patients treated for head and neck cancer in our study is 8%(n=90) at the end of six months and 16%(n=58) at the end of twelve months.

In a study of 378 patients treated for Head and Neck cancer, the incidence of post treatment hypothyroidism was 12.2%. The patients included in the study were divided into two groups, the first group patients (n=375) were evaluated retrospectively and the second group of patients (n=35) were evaluated prospectively.[78]

In a study of 198 patients treated for various Head and Neck cancer with combination of surgery and radiotherapy or surgery alone, the overall incidence of hypothyroidism after treatment was 15% with a median follow up of 12 months.[22]

Most of studies in the literature have considered increase in TSH level as a better marker for hypothyroidism than T3 and T4. In our study there is gradual decrease in T3 and T4 levels at 3, 6 and 1 year compared to pretreatment levels. In a group of ninety patients with various Head and Neck cancers, who underwent radiotherapy (EBRT), thyroid function tests were performed pretreatment and in the follow up period every monthly for about six months. There was increase in the TSH level compared to baseline (pretreatment) TSH level.[79] In our study there is significant increase in the TSH level at three months, six months and one year

compared to pretreatment levels (p=0.011,0.001,<0.0001). The median TSH level at three months, six months and one year is more compared to pretreatment levels, this shows that there is increase in TSH levels over time in the treatment of Head and Neck cancer.

Post treatment hypothyroidism is usually subclinical, which is not clinically obvious most of the time. In a prospective study of forty two patients with laryngeal and hypopharyngeal cancer who were treated by surgery and adjuvant radiotherapy, at the end of six months nine patients had subclinical hypothyroidism and one patient had clinical hypothyroidism.[21] In our study seven patients had subclinical hypothyroidism and two patients had clinical hypothyroidism, the overt hypothyroidism patient were those who were treated for laryngeal and hypopharyngeal carcinoma by surgery and adjuvant radiation.

The incidence of hypothyroidism, post treatment for Head and Neck cancer increases with the follow up period. Post treatment hypothyroidism may develop as early as one month and latency of onset may range from 16.8 months to 41.5 months.[80] In a study, 198 patients of various Head and Neck cancer were prospectively followed up for about three years with thyroid function tests at regular interval. Hypothyroidism was detected at an average period of 8 months.[22] In another prospective study of ninety five patients with early stage laryngeal cancer treated by radiotherapy were followed up with regular thyroid function tests, with average follow up period was 40 months, the projected incidence of post treatment hypothyroidism by Kaplan – Meier test at 5 years was 79% and the majority of patients developed hypothyroidism by 12 months.[55] In a randomized control study of 155 patients treated by primary radiotherapy and concurrent chemoradiation for various head and neck cancer, the projected incidence of post treatment

hypothyroidism by Kaplan-Meier test at the end of five years was 49%. The median time for patients to develop hypothyroidism was 1.4 years.[81] In our study, three patients developed hypothyroidism at the end of three months, four patients at the end of six months and two patients at the end of one year, among them more than 50% of the patients were detected within the first six months of treatment.

The incidence of hypothyroidism in the general population is more in females compared to males, this is seen even in hypothyroidism resulting from treatment of Head and Neck cancer.[41] In our study the incidence of hypothyroidism from treatment of Head and Neck cancer in females was 6% and in males it was 10%. This is in contrast to the general population. The high incidence of hypothyroidism in males is due to the higher number of male patients included in our study and most of them suffered from laryngeal and hypopharyngeal cancers, as against female patients who had oral cancer.

The morbidity arising due to treatment of Head and Neck cancer is more in older age group .In a meta- analysis by Vogelius its been observed that there is no association between the age and risk of development/ developing of hypothyroidism. In our study also there was no association between age and hypothyroidism.[41]

The incidence of hypothyroidism depends on the modality of treatment followed for Head and Neck cancer. The incidence of hypothyroidism from combined modality is higher compared to single modality. In our study 56.7% patients underwent surgery + adjuvant radiotherapy, 24.4% concurrent chemoradiation, 12.2% surgery+ adjuvant chemoradiation, 5.6% surgery alone and 1.1% EBRT alone. In our study patients treated with surgery and adjuvant radiotherapy had the highest incidence of post treatment hypothyroidism.

In a study involving 198 patients of different Head and Neck cancer, 136 patients were treated by surgery and adjuvant radiotherapy. After an average follow up of 12.1 months, 26 (19%) patients developed hypothyroidism (p=0.172). In our study 13.72% (7/51) patients had developed hypothyroidism following surgery and adjuvant radiation. But we couldn't find the statistical significance between the modality of treatment and hypothyroidism due to less number of patients treated by other modality and also a short follow up period.[22]

The incidence of hypothyroidism in case of laryngeal and hypopharyngeal cancer treated by surgery and adjuvant radiotherapy was higher compared to other Head and Neck cancers treated by same modality. The increased incidence of hypothyroidism is due to the fact that most of these patients undergo either lobectomy or total thyroidectomy and level six clearance during total laryngectomy. The incidence of hypothyroidism following treatment of laryngeal and hypopharyngeal cancer in our study was 33.33% (5/15) after a mean follow up of nine months.

In a study of seventy five patients with laryngeal cancer treated by surgery and adjuvant radiation, the incidence of hypothyroidism was 49.3% after a median follow up of 12 to 40 months. In this study they found an association between thyroid lobectomy and onset of post treatment hypothyroidism, however no association was established between radiation dose and hypothyroidism.[82]

In another study of forty two patients with laryngeal and hypopharyngeal cancer, who underwent surgery and/or adjuvant radiotherapy, who were followed up for six months. The incidence of hypothyroidism observed was 23.8%. This study showed a significant association between the hypothyroidism and factors like partial thyroidectomy, adjuvant radiation, bilateral neck dissection and level 6 dissection.[41]

There is paucity of literature about association between chemotherapy and post treatment hypothyroidism in Head and Neck cancer patients. In vitro studies have shown that cytotoxic drugs like cisplatin and 5 FU can have direct toxic effects on thyroctes, but there are no clinical studies to prove this so. Eventhough the chemotherapeutic drugs do n't have direct effect on thyroid gland, it can sensitize the gland to radiotherapy. In a study of 155 patients with various resectable, non-metastatic Head and Neck cancers, 100 patients were randomized into two groups. First group received only radiation and second group received concurrent chemoradiation. The remaining 55 patients were not randomized and they received concurrent chemoradiation. The projected incidence of hypothyroidism at the end of five years was 49% and eight years was 67% by Kaplan-Meier method. In this study they couldn't find a significant association between chemotherapy and hypothyroidism.[81] In our study one patient who received concurrent chemoradiation developed hypothyroidism (1/20) at the end of six months following treatment.

The treatment of Head and Neck cancer with newer drugs like tyrosine kinase inhibitors is in clinical trial (phase 3). Tyrosine kinase inhibitors are known to cause hypothyroidism due to inhibition of thyroid peroxidase activity, direct toxic effects on thyrocytes and impaired iodine uptake.

In a retrospective study of 206 patients of various Head and Neck cancer, 86 patient were treated by definitive RT, 83 patients by RT and neck dissection and 37 patients by total laryngectomy followed by adjuvant RT. After the median followup of 6.2 years, 22% of patients developed hypothyroidism at five years and 49% patients developed hypothyroidism at the end of ten years. There was statistically significant association between modality of treatment and hypothyroidism. But there was no association between age, overall stage of disease and hypothyroidism.[56]

In our study there was no association between modality of treatment, age, overall stage of the cancer and hypothyroidism. But there is a statistically significant increase in TSH levels at 3,6 and 1 year compared to pretreatment levels.

Conclusion

CONCLUSION:

- In Head and Neck cancer treated patients, there is statistically significant change in TSH (Thyroid Stimulating Hormone) levels at three months, six months and one year compared to pretreatment values.
- In Head and Neck cancer treated patients, the overall incidence of hypothyroidism at the end of six months is 8% and 16% at the end of one year.
- The frequency of developing hypothyroidism was highest at six months.
- The incidence of subclinical hypothyroidism was more compared to clinical hypothyroidism in patients treated for Head and Neck cancer hence thyroid function tests are advised at regular intervals for all head and neck cancer patients in the follow up period. This can minimize long term morbidity and facilitate better recovery of the tissues affected.
- There is requirement of more prospective studies with larger group of patients in each treatment modality, site of primary tumour, age group, stage to find out the risk factors for hypothyroidism and to make a schedule for thyroid function tests.

Summary

SUMMARY:

Ours is a prospective observational study done between December 2013 to July 2015 at R L Jallappa Hospital and Research centre, Tamaka, Kolar to find out the frequency and onset of hypothyroidism in patients treated for Head and Neck cancer by testing the thyroid function tests of the patients during pretreatment and at three months, six months and one year (where ever possible) in the follow up period.

Totally ninety patients were included in the study. The patients underwent treatment for various Head and Neck cancer either by single or multimodality treatment with surgery, radiotherapy and/or chemotherapy, thyroid function tests was done pretreatment and at regular intervals in the follow up period (three months, six months and one year wherever possible. In our study 63 patients had oral cavity carcinoma, 12 patients had oropharynx carcinoma, 10 patient had laryngeal and 5 patient had hypopharyngeal carcinoma. 58 patients had stage 4 disease and 29 patients had stage 3 disease. Fifty one patients underwent surgery and radiation, 22 patient concurrent chemoradiotherapy, 11 patients surgery and concurrent chemoradiation, 5 patients surgery and 1 patient radiotherapy. All patients (n=90) were followed up for six months and morethan 50% of patients (n=58) were followed up for one year.

At the end of three months of follow up three patients developed hypothyroidism, at the end of six months seven patients and at the end of one year nine patients developed hypothyroidism. There was statistically significant change in TSH values at three months, six months and one year compared to pretreatment values. The incidence of hypothyroidism is more in male patients. Majority of patients had subclinical hypothyroidism (n=7). The incidence of hypothyroidism was highest in laryngeal and hypopharyngeal carcinoma and surgery and adjuvant radiotherapy

group. There was statistically significant association between site of primary tumour and hypothyroidism at six months. In our study there was no association between age, stage of the tumour, modality of treatment and hypothyroidism.

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Annexure

ANNEXURES

OCCURANCE OF HYPOTHYROIDISM IN PATIENTS TREATED FOR HEAD AND NECK CANCER

Hospital No:

Name:
Age/Sex

Date:
Contact No:
Address:

Chief complaints:

Symptoms of hypothyroidism:

General : fatigue
Cold intolerance
Weight gain with poor appetite

Hair loss

Respiratory system : shortness of breath

Skin: paresthesia
Dry coarse skin

Intestine : constipation

Reproductive system: menorrhagia

Psychological : poor memory and concentration

Poor hearing

Pharynx and larynx: hoarseness of voice

CVS: slow pulse rate
Muscular system: delayed reflex relaxation

Extremities: coldness

Anaemia:

Past medical history: antithyroid drugs
Radioiodine ablation

Past surgical history:

Family history:

H/o allergies ;drugs/skin allergy/food

Examination:

General physical examination

Systemic examination:

CVS;

RS:

CNS:

ABDOMEN:

ENT Examination:
Ear:

Nose:

Oral cavity:

Oropharynx:

Neck examination:

Diagnosis : SITE SUBSITE AJCC TNM STAGING

Treatment details:

Surgery:

Radiation: Definitive

Adjuvant

Palliative

Chemotherapy : Neoadjuvant

Adjuvant

Palliative

THYRIOD PROFILE

Normal range	Pre treatment	3 months post treatment	6 months post treatment	1 year post treatment
T 3				
T 4				
TSH				

Folllow up:

complications:

INFORMED CONSENT

OCCURANCE OF HYPOTHYROIDISM IN PATIENTS TREATED FOR HEAD AND NECK CANCER

I have read this consent form/ has been read to me and I understand the purpose of this study, the procedures that will be used , the risks and benefits associated with my involvement in the study and the confidential nature of the information that will be collected and disclosed during the study.

I understand that I remain free to withdraw from the study at any time and this will not change my future care.

I have had the opportunity to ask questions regarding various aspects of the study and my questions have been answered to my satisfaction.

I, the undersigned agree to participate in this study and authorize the collection and disclosure of my personal information as outlined in this consent form.

Subjects/ guardians name and signature/ thumb impression date:

Name and signature of witness date:

KEY TO MASTER CHART

SEX

M-Male

F-Female

DIAGNOSIS

CA L BM- carcinoma left buccal mucosa

CA R BM- carcinoma right buccal mucosa

CA L Low alv- carcinoma left lower alveolus

CA L GBS- carcinoma left gengivo buccal sulcus

CA tongue- carcinoma anterior tongue

} Carcinoma oral cavity

CA oropharynx

CA Sup- carcinoma supraglottis

CA GLOTTIS

} carcinoma larynx

CA HyPH- carcinoma hypopharynx

S- surgery

RT- Radiotherapy

CT –chemotherapy

SERIAL NO	HOSPITAL NO	AGE	SEX	DIAGNOSIS	SIDE OF THE TUM	T	N	M	STAGE	TREATMENT	radiotherapy	chemotherap	RADIATION DOSE	TSH Before T	T3	T4	AT 3 MON	T3	T4	AT 6 MONT	T3	T4	AT 1 YEAR	T3	T4
1	973207	60	F	CA L BM	L	T3	N0	Mx	3	**S**	**RT**	-	60	3.73	1	5	1.77	1.1	5.2	1.7	1.1	5.6	2	0.7	5.2
2	960013	60	M	CA HyPH	-	T4a	N1	Mx	4	-	RT	CT	30	0.472	1.2	5.1	0.465	1.2	6	0.46	1.2	6	0.8	0.9	5
3	966182	50	F	CA R RMT	R	T3	N1	Mx	3	S	RT	CT	60	2.75	0.9	6	2.8	0.9	4.95	2.7	0.8	4.95	3	0.8	6.2
4	965585	64	F	CA L GBS	L	T4a	N1	Mx	4	S	RT	-	60	2.93	1.3	4.9	2.8	0.8	5.54	3	0.8	5.54	3.1	1	4.9
5	972988	50	M	CA L GBS	L	T4a	N1	Mx	4	S	RT	-	60	3.5	1.4	5.2	3.65	1.3	6.75	3	1.3	6.75	3	1.2	5.2
6	961620	55	F	CA L BM	L	T3	N2c	Mx	4	-	RT	CT	30	4.1	1.1	6	4	1.4	5.5	3.8	1.4	5.5	-	-	-
7	857783	65	F	CA L BM	L	T4a	N2a	Mx	4	S	RT	CT	60	1.6	1.2	4.95	2	0.8	5.4	2.1	0.8	5.4	1.9	0.9	4.9
8	978123	45	F	CA L BM	L	T4a	N1	Mx	4	S	RT	-	60	1.53	0.9	5.54	1.45	1.5	4.9	2	1.4	4.9	1.8	**1.2**	5.54
9	976387	49	M	CA R BM	R	T4a	N2b	Mx	4	S	RT	-	60	4	0.8	6.75	4.1	1.3	5.1	4	1.3	4.8	3.9	**1.3**	6.75
10	984928	65	F	CA HyPH	-	T3	N2b	Mx	4	-	RT	CT	30	3.97	1.3	5.5	3.9	1.4	5.2	4	1.5	5.2	3.5	**1.4**	5.4
11	978895	68	F	CA R BM	R	T3	N1	Mx	3	S	RT	-	45	3.4	1.4	5.4	3.8	1.3	6.2	4	1.3	6.2	12	**0.8**	5.3
12	857518	70	M	CA Sup	-	T3	N1	Mx	3	S	RT	-	66	3.5	0.8	4.9	73.6	0.2	4	-	-	-	-	-	-
13	993530	40	F	CA Lat Tongue	L	T3	N1	Mx	3	S	RT	-	66	4.03	1.5	5.1	1.77	1.4	4.95	8	1.4	4.95	-	-	-
14	992684	60	F	CA L GBS	L	T3	N1	Mx	3	S	RT	-	66	3.06	1.3	5.2	4	0.8	7.25	3.5	0.8	7	4	**0.9**	5.2
15	986743	50	M	CA Lat Tongue	R	T4a	N1	Mx	4	-	RT	CT	66	2.56	1.4	6.2	2.7	1.2	4.8	2.9	1.3	4.8	3	**1.2**	6.1
16	994373	53	M	CA R BM	R	T3	N2a	Mx	4	S	RT	-	66	2.68	1.3	6.5	3	1.5	6.1	3.5	1.5	5.9	4	**1.3**	6.4
17	866767	65	M	CA Sup	-	T4a	N0	Mx	4	-	RT	CT	66	3	1.2	4.95	3.5	1.7	7	3.7	1.8	7	3.8	**1.4**	4.95
18	949884	38	M	CA R BM	R	T4a	N2a	Mx	4	S	RT	CT	66	2.94	1.4	7.25	2.9	1.1	6.9	3	1.1	6.9	3.1	**1.5**	7.23
19	986014	30	M	CA Lat Tongue	L	T4a	N1	Mx	4	S	RT	CT	66	3.17	0.8	4.8	4	1	5.5	3	1.5	5.5	-	-	-
20	991117	28	F	CA L BM	L	T4a	N1	Mx	4	S	RT	-	66	1.07	1.2	6.1	1	0.9	5.4	1.5	0.9	5.3	1.4	**0.9**	6
21	992379	75	F	CA R BM	R	T4a	N1	Mx	4	S	-	-	-	3.76	1.5	7	4	1.3	5.7	3.2	1.3	5.7	3.7	**0.8**	7.2
22	925665	60	F	CA L BM	L	T2	2b	Mx	4	S	RT	-	60	3.35	1.7	6.9	3.3	1.4	5.4	3.45	1.4	5.2	4	**0.9**	6.9
23	989511	65	F	CA R BM	R	T4a	N1	Mx	4	S	RT	-	66	3.81	1.1	5.5	3.6	1.3	5.6	3.65	1.2	5.6	3.45	**1.2**	5.3
24	985005	44	F	CA L BM	L	T4b	N0	Mx	4	-	RT	CT	66	3.26	1	5.4	3.2	1.1	6	3.25	1.1	6.3	-	-	-
25	972713	40	M	CA L BM	L	T3	N2a	Mx	4	S	RT	-	60	3.85	0.9	5.7	3.8	1	4.95	3.85	1	4.95	4	**1.3**	5.5
26	989683	55	M	CA Sup	-	T4a	2b	Mx	4	S	RT	-	60	4	1.3	5.4	4.1	1.4	5.1	30	1.3	5.1	-	-	-
27	988851	70	M	CA L BM	L	T4a	N0	Mx	4	S	RT	-	66	4	1.4	5.6	4.1	1.3	8	3.8	1.5	7.3	4.1	**1.5**	5.4
28	997847	60	F	CA L Low alv	L	T4a	N1	Mx	4	S	RT	-	66	3.69	1.3	6	4	1	7.9	3.5	1	7.9	4.1	**1.6**	6
29	1246	55	F	CA R Low alv	R	T4a	N2b	Mx	4	S	RT	-	66	0.726	1.1	4.95	0.8	0.9	7.8	1.05	0.9	7.8	1.1	**1.2**	4.95
30	10048	65	F	CA L BM	L	T4a	N2b	Mx	4	S	RT	-	66	1	1	5.1	1.05	1.6	6.8	2	1.6	6.8	1.8	**1.3**	5.1
31	869	40	F	CA R BM	R	T3	N0	Mx	3	S	-	-	-	4.1	1.4	8	4	1.3	4.95	4.05	1.4	5.2	4.15	**1.4**	8
32	5642	35	F	CA L BM	L	T3	N1	Mx	3	S	RT	-	46	2.02	1.3	7.9	2.45	1.2	5	3	1.2	5	2.9	**0.8**	7
33	984482	46	M	CA Lat Tongue	L	T2	N2b	Mx	4	S	RT	CT	46	1.69	1	7.8	1.8	1.1	5.5	2	1.3	5.5	1.5	**0.9**	7.8
34	1001563	38	M	CA R BM	R	T4a	N2b	Mx	4	S	RT	CT	66	2	0.9	6.8	3	1.3	5.7	3.1	1.3	5.7	3.15	**0.7**	6.5
35	994289	65	M	CA oropharynx	-	T3	N1	Mx	3	-	RT	CT	66	1.05	1.6	4.95	1.3	1.4	6.1	1.5	1.4	6.1	2	**0.9**	4.95
36	1002042	70	M	CA R BM	R	T4b	N2b	Mx	4	-	RT	CT	30	3.2	1.3	5	3	1.5	6.2	3.1	1.5	6.2	-	-	-
37	1001077	35	F	CA L BM	L	T1	N0	Mx	1	S	-	-	-	4.05	1.2	5.5	4.1	1	5.9	4.15	1.3	5.9	4.1	**1.2**	5.5
38	998486	58	M	CA R BM	R	T4a	N1	Mx	4	S	RT	-	66	2.51	1.1	5.7	3.5	0.9	5.8	3.9	0.9	5.8	4.05	**1.3**	5.7
39	74144	60	M	CA oropharynx	-	T3	N1	Mx	3	-	RT	CT	66	4.01	1.3	6.1	3.9	1.7	6	3.8	1.7	6	4	**1.4**	6.3
40	75432	50	F	CA L BM	L	T3	N1	Mx	3	S	RT	-	66	3.62	1.4	6.2	4	13	6.2	4.05	0.8	6.2	4.15	**1.5**	6.2
41	77216	45	F	CA L BM	L	T4a	N1	Mx	4	S	RT	-	66	2.43	1.5	5.9	3.05	1.1	5	3.1	1.1	5	3.5	**1.6**	5.5
42	823227	68	M	CA Sup	-	T4a	N2b	Mx	4	-	RT	CT	60	2	1	5.8	1.8	1.2	5.5	3	1.2	5.5	4	**1.2**	5.8
43	63671	45	M	CA Lat Tongue	R	T2	N1	Mx	3	S	RT	-	66	1.91	0.9	6	2.05	1	6.1	2.5	1	6.1	3	**1.3**	6
44	48308	65	M	CA Glottis	-	T3	N0	Mx	3	S	RT	-	66	4.05	1.7	6.2	4.1	0.9	7	3.9	0.9	7	3.8	**1.2**	6.2
45	77147	52	M	CA R BM	R	T4a	N2b	Mx	4	S	RT	-	66	4	13	5	3.5	1.2	5.8	3.65	1.2	5.8	4	**0.9**	5
46	77216	45	F	CA L BM	L	T3	N0	Mx	3	S	RT	-	66	2.43	1.1	5.5	2.53	1.3	5.9	2.6	1.3	5.9	3	**0.8**	5.5
47	89014	45	F	CA L BM	L	T2	N2a	Mx	4	S	RT	-	66	3.52	1.2	6.1	3.4	1.4	5.8	3.57	1.4	5.8	4	**1.1**	6.3
48	1019648	62	F	CA oropharynx	-	T4a	N1	Mx	4	-	RT	CT	66	0.95	1	7	1.2	1.5	5	1.3	1.4	5	2	**1.2**	6.9
49	1020168	60	F	CA L BM	L	T3	N0	Mx	3	S	-	-	-	4.13	0.9	5.8	4	1.6	5.8	4.05	1.6	5.8	4	**1.3**	5.5
50	945850	55	F	CA L BM	L	T3	N2a	Mx	4	S	RT	CT	60	3.05	1.2	5.9	3	1.3	4.8	2.9	1.3	4.8	3	**1.4**	6.2
51	52764	55	F	CA L BM	L	T4a	N1	Mx	4	S	RT	-	66	3	1.3	5.8	3.05	1.2	5.3	2.85	1.3	5.3	3	**1.5**	5
52	60032	70	M	CA Glottis	-	T3	N0	Mx	3	S	RT	-	66	2.86	1.4	5	3	1	5.5	36	1	5.5	-	-	-
53	61832	55	M	CA HyPH	-	T4a	N1	Mx	4	S	RT	-	66	3.69	1.5	5.8	30.3	0.3	3.9	-	-	-	-	-	-
54	1004604	65	F	CA L BM	L	T4a	N2c	Mx	4	S	RT	-	66	2.06	1.6	4.8	2.3	1.4	4.9	2.9	1.4	4.9	3	**1.2**	4.9
55	1002279	50	M	CA HyPH	-	T4a	N1	Mx	4	S	RT	-	45	3.9	1.3	5.3	3.8	1.5	5.3	3.75	1.5	5.3	3.5	**1.3**	5.2
56	1002102	55	F	CA R BM	R	T2	N0	Mx	3	S	-	-	-	1.3	1.2	5.5	1.45	1.6	5.7	1.37	1.3	5.7	2	**1.2**	5.4
57	1018950	50	M	CA Sup	-	T2	N0	Mx	3	S	RT	CT	-	2.9	1	5.7	3	1	5.8	2.8	1	5.8	-	-	-
58	1003707	64	M	CA oropharynx	-	T4a	N2a	Mx	4	-	RT	CT	66	3.9	1.2	4.9	4.1	1.2	6.1	4	1.2	6.1	-	-	-
59	41893	55	F	CA L BM	L	T4a	N0	Mx	4	S	RT	-	66	4	1.4	5.3	4.1	1.3	6.3	4	1.3	6.3	-	-	-
60	1004708	70	M	CA Sup	-	T3	N1	Mx	3	-	RT	-	66	3.5	1.5	5.7	4	1.4	5.1	3.5	1.4	5.1	-	-	-
61	38564	42	M	CA R BM	R	T4a	N1	Mx	4	S	RT	-	66	3.8	1.6	5.8	4.12	1.5	4.95	3.5	1.5	4.95	-	**1.2**	5.5
62	1019507	50	M	CA Lat Tongue	-	T2	N1	Mx	3	S	RT	-	66	4.1	1	6.1	3.8	1.2	4.6	4.15	1.2	4.6	-	-	-
63	46773	41	M	CA L Low alv	L	T2	N0	Mx	3	S	RT	-	60	3	1.2	6.3	3.2	1	4.8	3.1	1	4.8	-	-	-
64	7434	70	F	CA oropharynx	-	T2	N0	Mx	3	-	RT	CT	66	3.5	1.3	5.1	3.8	0.9	5.5	11	0.9	5.5	-	-	-
65	24807	65	M	CA R BM	R	T3	N1	Mx	3	S	RT	-	45	2.7	1.4	4.95	2.9	0.8	7.1	3	0.8	7.1	-	-	-
66	32554	50	M	CA oropharynx	-	T4a	N3	Mx	4	-	RT	CT	66	4	1.5	4.6	3.8	1.3	8	3.5	1.3	8	-	-	-
67	3025	65	M	CA Sup	-	T3	N1	Mx	4	-	RT	CT	30	2.8	1.2	4.8	3	1.4	7.5	3.3	1.4	7.5	-	-	-
68	6539	57	M	CA HyPH	-	T4a	N2c	Mx	4	S	RT	-	66	3.5	1	5.5	7	1.5	6.1				-	-	-
69	1005763	45	M	CA oropharynx	-	T4a	N1	Mx	4	-	RT	CT	66	3.5	0.9	7.1	2.9	1.6	5.8	3	1.6	5.8	-	-	-
70	972988	50	M	CA L BM	L	T4a	N1	Mx	4	S	RT	-	45	4	0.8	8	3.2	1.7	4.95	3.4	1.7	4.95	-	-	-
71	22307	58	M	CA L Lat Tongue	L	T2	N0	Mx	2	S	RT	-	66	3	1.3	7.5	3.8	1.5	5.1	4	1.5	5.1	-	-	-
72	76370	56	F	CA L BM	L	T3	N2a	Mx	4	S	RT	CT	60	3.7	1.4	6.1	3.9	1.2	5.9	4	1.2	5.9	-	-	-
73	60014	60	F	CA L BM	L	T4a	N1	Mx	4	S	RT	-	66	2.8	1.5	5.8	2.5	1.2	5.8	3.4	1.2	5.8	-	-	-
74	81167	55	M	CA oropharynx	-	T2	N2a	Mx	4	-	RT	CT	66	4.1	1.6	4.95	4.05	1.3	4.95	3.9	1.3	4.95	-	-	-
75	4880	50	F	CA LBM	L	T3	N0	Mx	3	S	RT	-	66	2.9	1.7	5.1	3	1.4	6.1	3.2	1.4	6.1	-	-	-
76	56738	40	F	CA L BM	L	T2	N0	Mx	2	S	RT	-	66	3.4	1.5	5.9	3.5	1	5.9	4	1	5.9	-	-	-
77	1019648	62	F	CA oropharynx	-	T4a	N1	Mx	4	-	RT	CT	66	3	1.2	5.8	3.5	0.9	4.95	4	0.9	4.95	-	-	-
78	997841	60	F	CA L Lower al	L	T4a	N1	Mx	4	S	RT	-	45	2.9	1.2	4.95	3	0.8	8	3.1	0.8	8	-	-	-
79	81160	50	F	CA L BM	L	T4a	N0	Mx	4	S	RT	-	60	3.3	1.3	6.1	2.9	0.9	7.5	3	0.9	7.5	-	-	-
80	28665	40	F	CA R BM	R	T4a	N1	Mx	4	S	RT	-	66	4	1.4	5.9	3.9	1.2	5.5	3.5	1.2	5.5	-	-	-
81	7535	50	M	CA oropharynx	-	T3	N1	Mx	3	-	RT	CT	66	3.3	1	4.95	3.2	1.3	5.45	4	1.3	5.45	-	-	-
82	42445	55	F	CA Sup	-	T4a	N1	Mx	4	S	RT	-	66	1.6	0.9	8	1.8	1.4	5.5	2	1.4	5.5	-	-	-
83	7035	50	M	CA HyPH	-	T4a	N1	Mx	4	-	RT	CT	66	3.6	0.8	7.5	3	1	5.45	2.9	1	5.45	-	-	-
84	7536	54	M	CA oropharynx	-	T4a	N1	Mx	4	-	RT	CT	66	4	0.9	5.5	3.5	1.1	5.6	3.6	1.1	5.6	-	-	-
85	44308	56	M	CA L Lat Tongue	L	T3	N1	Mx	3	S	RT	-	66	2	1.2	5.45	2.5	0.85	6	2.7	0.85	6	-	-	-
86	86730	49	M	CA L BM	L	T4a	N1	Mx	4	S	RT	-	66	4	1.3	5.5	4.01	1.2	6.1	3.45	1.2	6.1	-	-	-
87	76564	55	F	CA R BM	R	T3	N2a	Mx	4	S	RT	CT	66	3.7	1.4	5.45	3.55	1.3	5.5	3.45	1.3	5.5	-	-	-
88	56456	53	M	CA oropharynx	-	T3	N1	Mx	3	-	RT	CT	66	2.8	1	5.6	2.65	1.4	5.3	3	1.4	5.3	-	-	-
89	841826	49	M	CA R Lat Tongue	R	T3	N1	Mx	3	S	RT	CT	60	3.3	1.1	6	3	1.5	5.2	3.6	1.5	5.2	36.3	**1.1**	5.8
90	12385	45	M	CA R BM	R	T3	N1	Mx	3	S	RT	-	66	3.4	0.9	6.1	3.1	1.6	5.6	3	1.6	5.6	-	-	-