PATTERN AND DETERMINANTS OF EARLY THYROID HORMONE PROFILE CHANGES FOLLOWING RADIOTHERAPY FOR HEAD AND NECK CANCERS AT THE KENYATTA NATIONAL HOSPITAL.

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A dissertation submitted in partial fulfilment of the requirements for the Degree of Master of Medicine in Otorhinolaryngology, Head and Neck Surgery, University of Nairobi

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ABBREVIATIONS

2D	2 Dimension
3D	3 Dimension
DIT-	Di-IodoThyronine
DNA-	DeoxyriboNucleic Acid
EBRT-	External Beam Radiotherapy
ENT-	Ear, Nose and Throat
FT3	Free Triiodothyronine
FT4-	Free Tetra iodothyronine
HLA-DR-	Human Leukocyte Antigen-DR isotype
ICD-	International Classification of Diseases
KNH-	Kenyatta National Hospital
LINAC	Linear Accelerator
MIT-	Mono IodoThyronine
PBCR-	Population Based Cancer Registry
SPSS-	Statistical Package for Social Sciences
T3-	Triiodothyronine
T4-	Tetra iodothyronine
TBG-	Thyroxine Binding Globulin
TD-	Tolerance Dose
TNM-	Tumour Node Metastasis
TRH -	Thyrotropin Releasing Hormone
TSH-	Thyroid Stimulating Hormone

ABSTRACT

Background: Head and neck cancers are ranked as the 3rd commonest cancers globally. Majority of the cancers (60%) are treated with radiotherapy. The thyroid gland is one of the organs at risk of damage due to the effects of neck irradiation. Thyroid gland dysfunction can occur early or late and increase the morbidity.

Objective: This study evaluated the pattern and determinants of early changes in thyroid hormone profiles following radiotherapy for head and neck cancers at the Kenyatta National Hospital.

Methodology: This was a prospective observational study of 50 patients with head and neck cancers who were treated with radiotherapy at the Kenyatta national hospital. Convenience sampling technique was used to recruit patients. Data collection tool captured demographics, clinical and disease characteristics, treatment modality, pre-treatment and three months post radiotherapy thyroid function test results.

Data management and analysis: Data was expressed as means and standard deviations. Analysis of variance was used to determine type of thyroid dysfunction at three months post radiotherapy with a p value of <0.05 being significant. Exact fisher test was used to correlate variables and development of thyroid dysfunction with a p value of < 0.05 being significant.

Results: Results of fifty patients was analysed which constituted 31(62%) males, and 19 (38%)females. The mean age was 52.4±16.6 years with an age range of 18-82 years. Thyroid dysfunction occurred in 2(4%) patients before commencement of radiotherapy. Fifteen patients (30%) had thyroid dysfunction at three months after completion of radiotherapy. This comprised 6(12%) patients with subclinical hypothyroidism, 6(12%) patients with clinical hypothyroidism,1(2%) patient with subclinical hyperthyroidism ,2(4%) patients with clinical hyperthyroidism. There was significant change in FT3(2.94±0.72) to (2.96±0.84) after radiotherapy with a p value of <0.04. Chemotherapy and the degree of differentiation of tumour influenced development of thyroid dysfunction with a p value of < 0.03 and 0.04 respectively. Age, gender, cancer subsite, TNM stage, radiotherapy machine type, duration of treatment had no-significant influence on development of thyroid dysfunction with a p value > 0.05.

Conclusion: The thyroid gland is affected by radiotherapy during treatment of head and neck cancers. Thyroid hormones were found to increase at three months. Chemotherapy and degree of differentiation of the tumour were the key determinants in development of thyroid dysfunction. We therefore recommend long term follow up of these patients to see if the patterns of thyroid profile would remain the same or change. We also recommend further studies with larger sample size to see the trends in thyroid hormone changes. We also recommend routine thyroid functions tests pre and post radiotherapy.

1.0 CHAPTER ONE: INTRODUCTION

The incidences of head and neck cancers in the world are on an upward trend due to changes in lifestyle such as, increase in the number of cigarettes smokers, increase in alcohol consumption, emerging oropharyngeal infections with human papilloma virus amongst other risk factors.(1) Global cancer statistics of 2018 ranked head and neck cancers as the 3rd commonest cancers in the world.(2) Head and neck cancers constitute 5.7% of cancer burden in Kenya3). The sites of origin of head and neck cancers include the upper aero-digestive tract, salivary glands, thyroid and parathyroid glands. Majority of head and neck cancers arise from mucosal lining of the upper aero-digestive tract, of which more than 90% are squamous cell carcinomas. The sites of the upper aero digestive tract where these cancers arise from include the oral cavity, oropharynx, hypopharynx, larynx, nasopharynx, nose and paranasal sinuses.(4) Nasopharyngeal carcinoma is the commonest head and neck cancer in Kenya in the 2020 GLOBOCAN updates.(5)

1.1 Treatment of Head and Neck Cancers

Different ways of treating head and neck cancers exist; treatment can either be single modality or multi-modality. Single modality can either be radiotherapy, surgery or chemotherapy. Multi-modality treatment includes surgery followed by adjuvant radiotherapy with or without chemotherapy or chemo-radiotherapy. Treatment is done with intent of either curing the disease or palliation.

1.2Radiotherapy for Head and Neck Cancers

Radiotherapy is used to treat approximately 60% of all cancers of the head and neck(5). Its advantages over surgery include its ability to preserve anatomical organs of the upper aero-digestive tract like pharynx and larynx. Anatomical organ preservation cannot be equated to organ functional preservation and these two are different and cannot be used interchangeably. Preservation of function involves preservation of both physiological functions of body systems and psychological functions.(6)

Unlike surgery radiotherapy has the advantage of function preservation, some of the functions preserved include swallowing, phonation and speech.[7] Radiotherapy destroys tumour cells by causing damage to the DNA(deoxyribonucleic acid) either unswervingly when radiation is absorbed by the DNA itself causing ionisation of atoms of the DNA and hence causes damage. The indirect mode of damage of the DNA involves formation of intermediate ions which produces intermediate free radicals. The intermediate free radicals cause breaks of chemical bonds of the DNA ultimately resulting in mitotic death. Other mechanisms radiation damage tumour cells include apoptosis and cell cycle arrest.[7]

The external beam radiotherapy (EBRT) is the generally frequently used type of radiotherapy in head and neck cancers. Conventionally, EBRT is delivered in fractions of 1.8-2.0 Grays per day for five days in a week with allowance of two days over the weekend for resting, for a total of 35 days to make a total of between 63 to 70 Grays. There are also altered fractionation schedules such as hyper fractionation and accelerated fractionation. In hyper-fractionation schedules radiotherapy is administered in two divided fractions per day of smaller doses of between 1.1 to 1.2 Grays per fraction with the general time of treatment being the same as for conventionally delivered course of radiotherapy. Accelerated fractionation is delivered in larger radiation doses multiple times in a day with the aim of reducing treatment time and prevention of tumour re-population. Advancement in radiation technologies such as 3D-conformal radiotherapy, intensity modulated radiotherapy, image guided radiotherapy, neutron and carbon ion therapy, proton therapy and brachytherapy has enabled delivery of higher radiotherapy doses to the tumour and other target areas without causing injury to the surrounding tissues and organs.[5]

1.3 Thyroid Gland

1.3.1 Anatomy and Physiology of Thyroid Gland

Thyroid gland is an endocrine gland found in the anterior part of the neck. The two symmetrical lobes are united in the midline by an isthmus that lies anterior to 2nd, 3rd and 4th tracheal rings. The lobes are found on either side of the larynx and trachea spanning from the oblique line of the thyroid cartilage to the sixth tracheal rings. The gland weighs about 25 grams and is highly vascularised receiving blood supply from the superior and inferior thyroid arteries.[8]

The thyroid gland is organised into thyroid follicles which forms the functional unit of the gland. Each thyroid follicle consists of follicular cells surrounding a central mass of colloid and are responsible for the production of thyroid hormones. There are also Para follicular cells also known as C cells located between two adjacent thyroid follicles that produce calcitonin.

The thyroid gland primarily functions to secrete thyroid hormones which include tetra iodothyronine (T4), tri-iodothyronine (T3) and calcitonin. Iodine is important in formation of thyroid hormones. Within the follicular cell lumen iodine undergoes iodination to iodide which is incorporated into thyroglobulin molecule to form mono iodothyronine(MIT) and di-iodothyronine(DIT). Coupling of MIT and DIT forms T3 which is hormonally active, while coupling of two molecules of DIT forms T4. Both T3 and T4 are bound to thyroxine binding globulin(TBG) in circulation. The true thyroidal hormonal status in circulation is best evaluated by measuring the free hormone levels in circulation (FT3, FT4) rather than the total levels.

Hypothalamus releases thyrotropin releasing hormone(TRH) that influences on the anterior pituitary gland to generate thyroid stimulating hormone(TSH). TSH acts on the thyroid gland by increasing circulation and trapping of iodine with subsequent production of thyroid hormone. High circulating levels of thyroid hormones acts in a negative feedback mechanism on the anterior pituitary gland and hypothalamus respectively and hence reduce secretion of TSH and TRH respectively and hence lower thyroid hormones secretion by the thyroid gland. Some of the crucial roles of thyroid hormones in human body include regulation of metabolism, stimulation of oxygen consumption by cells, regulation of lipid and carbohydrate metabolism which influences body mass and mentation.[9]

1.4 Radiation Induced Thyroid Dysfunction

During neck irradiation the thyroid gland will be exposed to the therapeutic radiation dose by virtue of it being located in the field of radiation. The gland is not radio resistant as previously thought and will absorb radiation doses which will have a detrimental effect on the gland. Responses of normal tissue to therapeutic irradiation was studied by Emami et al[10] where the thyroid gland was found to have different tolerance doses (TD) at different Grays. Receiving 45 Grays had a probability of getting 8% complications within five years of treatment whereas receiving 60 and 70 Grays had a probability of 13% and 35% complications respectively within five years.[10])

Radiation induced thyroid injury can be divided into acute, sub-acute and late injuries. Acute or early changes are defined as changes that occur from completion of radiotherapy up to the first three months.[11]Sub acute changes occur from three months up to one year and late changes are changes observed after one year.[12] Acute and sub-acute injuries are thought to occur due to thyroid parenchyma cell damage while late effects results from vascular damage.[13]Radiotherapy causes damage of small blood vessels of the thyroid gland and the gland capsule with its septae as a result of radiotherapy induced fibrosis. This results in impairment of compensatory gland hypertrophy after thyroidectomy.[14][15]

Irradiation to the neck also causes atherosclerosis of the carotid arteries which interferes with blood supply to the thyroid gland, this will cause ischemia of the thyroid gland and subsequently lead to thyroid dysfunction.[16]

Radiotherapy also causes auto immunity to normal thyroid tissue via several mechanisms. One of the mechanisms is that radiotherapy causes cell death which releases antigens that stimulate immunity. Another mechanism is that radiotherapy causes cell damage with consequent surface expression of aberrant HLA-DR genes or specific thyroid antigens that induce immunity. Following Cell damage, the residual cells undergoes secondary hyperplasia and are thought to contribute to thyroid dysfunction[17]. Autoimmune reaction against thyroid tissue results in elevated levels of anti-thyroid antibodies (anti-thyroglobulin antibodies and anti-microsomal antibodies). Elevated levels of auto antibodies are associated with thyroid cancer, goitre and Hashimoto thyroiditis.[18]

Besides vascular damage, thyroid parenchyma cell injury and auto immune reactions, thyroid dysfunction can also occur as a result of radiation injury to the hypothalamus and pituitary gland which will cause secondary hypothyroidism as a late effect.[19]

Concurrent use of chemotherapy with radiotherapy is expected to increase radio-sensitivity of thyroid gland to the effects of radiotherapy and increase the incidences of thyroid dysfunctions, However several studies done have revealed that use of chemotherapy has no effect on the thyroid gland.[20][21][22]

There are several radiotherapy induced thyroid disorders. They include hypothyroidism, hyperthyroidism, Hashimoto thyroiditis, benign adenoma, grave's disease and thyroid cancer.[23]Among these hypothyroidism is the most common complication with an incidence of 20-30%.[14]

Hypothyroidism will manifest with several symptoms which may worsen the already existing disease of head and neck cancer. Some of the symptoms include fatigue, cold intolerance, dry skin, facial puffiness, constipation, low pitch voice, depression and cognitive impairment.[24]
Physical impairment manifestations include decreased basal metabolic rate, decreased cardiac output, decreased heart rate, decreased ventilation rate. Thyroid hormones promotes wound healing and some consequences of hypothyroidism includes delayed wound healing which may results in higher risks of salivary fistula after laryngectomy.[25]
Hyperthyroidism patients present with symptoms due to hyper adrenergic activity which include palpitations, anxiety, diaphoresis, heat intolerance. Hyper metabolism will cause weight loss, increased appetite and fever. Neuromuscular manifestations include weakness of the proximal muscles. Neuropsychiatric manifestations include anxiety, insomnia and psychosis. Ocular manifestations include exophthalmos and increased lacrimation. Cutaneous manifestations include onycholysis, hyperpigmentation and pretibial myxedema.[26]

2.0 CHAPTER TWO: LITERATURE REVIEW

Thyroid dysfunction is a common complication after external beam radiotherapy to treat head and neck cancers.[27][28] Measurement of TSH,T4,T3 in serum is vital to diagnose overt and sub-clinical thyroid dysfunction. The individual test outcome is compared to the reference ranges of the laboratory. The test result is subject to biologic variation and analytic variation.[29]Biologic variation is grouped into two sets namely, variation between individuals and variation in the individual. Variation between individuals comes as a result of different set points around which each individual varies while individual variation is characterised by rhythmic aberrations of multiple occurences. Several factors determine biologic variation in thyroid function tests.[30] Some of the factors include circadian variation where TSH is found to be high at midnight but low during the day. T3 and T4 show no variations despite the TSH surge at night. Other factors include seasonal variations where T3 is found to be high during cold season while T4 and TSH seasonal changes are less inconsistent. Iodine intake, gender, protein concentration in serum, prolonged veni-pressure and posture during phlebotomy alter concentration of T3 and T4 slightly in serum but the effect is small. Drugs, smoking, pregnancy also influence level of TSH and thyroid hormones. These variations don't go beyond the normal standard ranges and they contribute to the width of the reference ranges.[30] Analytical variations are variations that result from analytical errors. To evaluate significance of change in serial results of thyroid function tests, test results are subjected to delta check method which include delta difference, delta percent change, rate difference and rate percent change.[31] A delta percent change above 95% or below 5% in the normal distribution curve will constitute a significant change over time. Some of thyroidal dysfunction diagnosed using biochemical test include hypothyroidism and hyperthyroidism which can either be clinical or sub-clinical.

Clinical hypothyroidism is characterised by high TSH levels and low T4 and T3 levels, subclinical hypothyroidism is characterised by high TSH levels and normal T4 or T3 levels. Hyperthyroidism though rare has also been reported to occur. This is characterised by elevated levels of T3 and T4 with low levels of TSH. Subclinical hyperthyroidism is characterised by low levels of TSH and normal levels of T3 and T4. Thyroid dysfunction following radiotherapy for treatment of head and neck cancers is thought to be influenced by several variables like radiotherapy dose, age, gender, chemotherapy, type of neck dissection whether radical or selective, performance of hemi-thyroidectomy, tumour stage according to TNM, degree of differentiation of the tumour.

Several studies either retrospective or prospective have been done to evaluate the effect of radiotherapy on the thyroid gland. Majority of the retrospective studies however lack pre-treatment thyroid functions values. Mehmet et al[31] evaluated 47 patients prospectively for early thyroid dysfunction on completion of neck EBRT either as primary treatment or adjuvant treatment after surgery. The levels of thyroid hormones (TSH, FT4, FT3) were evaluated before commencement of EBRT and immediately after completion of EBRT. The duration of EBRT was between 35-49 days and the average dose of EBRT was 64 Grays with a range of 50-70 Grays. There was a considerable fall in TSH levels after completion of radiotherapy in both the operated and non-operated patients (p value<0.05). There was also a major fall in FT3 and a rise in FT4 in both groups of patients (p value<0.05). TSH levels was drastically lower in the non-operated group unlike the operated group at conclusion of radiotherapy in spite of both groups receiving similar dose of radiotherapy (p value<0.05), 14% (n=7) developed subclinical hypothyroidism in both groups while 10% (n=5) developed hyperthyroidism. These two group of patients were however asymptomatic. Some of the limitations of this study included lack of subsequent follow up following completion of EBRT, whether patients received chemotherapy or not is also not mentioned in the study.

Madhani et al[32] studied acute thyroid profile changes in 30 patients undergoing external beam irradiation of neck for treatment of head and neck cancers. The dose of radiotherapy given was 60 Grays for post-operative patients and 70 Grays for in operable tumours at 2 Grays per fraction five times in a week. Thyroid functions were done before commencement of treatment, at four weeks during treatment, on finishing treatment, one month after finishing treatment and at four months after treatment conclusion. The levels of FT3 and FT4 increased after four weeks of treatment and then started decreasing on completion of treatment, at one month and at four months after completion of treatment. TSH decreased after four weeks and then gradually increased. The mean values of T3, T4, and TSH differed statistically significant between different time points they were analysed during and after radiotherapy (p value < 0.001). One of the limitation of this study was the small number of sample size. In contrast Chougule et al [33] studied 90 patients undergoing external beam radiotherapy (EBRT). Thyroid functions were conducted before treatment, mid-way during EBRT, after completion of EBRT and subsequently monthly for six months. The findings from this study indicated that serum T3 and T4 levels were reduced at completion of EBRT and maintained the same level after six months of follow up. Serum levels of TSH however did not notably vary between time points. Decrease in level of serum T3 and T4 was evident in poorly differentiated tumours followed by well differentiated tumours and moderately differentiated

tumours. According to Srinkatia et al[34] ,45 patients over nine months period were investigated on how common hypothyroidism was after EBRT to the neck in head and neck cancer patients. Patients received radiation dose of more than 40 Grays with concurrent chemotherapy. They found a total of 31.1% of the patients had clinical hypothyroidism, 11.1% had sub-clinical hypothyroidism therefore 42.2% developed radiation induced hypothyroidism. In their study chemotherapy was found to have no effect on the thyroid gland as hypothyroidism was found in equal measure in patients who received concurrent chemo-radiotherapy and those who received radiotherapy alone. They found age to be a determinant in the occurrence of hypothyroidism as hypothyroidism was found among the elderly when compared with the young. Hypothyroidism was also more common in the female gender because female have small thyroid volume compared to men an observation also found by Alterio et al.[23] Radiotherapy dose was not a significant contributor to development of hypothyroidism related to a retrospective study by Capoglu et al [11] who evaluated 63 patients retrospectively to determine early and delayed changes of thyroid dysfunction after radiation therapy for head and neck cancers either with or without surgery. Some of the variables studied and their influence on development of thyroid dysfunction included age, gender, surgical operation, smoking history, total neck dose, stage of the disease and con-current chemotherapy. Among these variables there was none which was found to be a risk factor for the development of hypothyroidism. However, 38% (n=24) of the patients developed radiation induced hypothyroidism that is 12.7% (n=8) with clinical hypothyroidism and 25.4% (n=16) with subclinical hypothyroidism. The median time to development of clinical hypothyroidism was 15 months and subclinical hypothyroidism was 3 months. Sub-clinical hyperthyroidism was found in 17.5% (n=11) with a median time to development of sub-clinical hyperthyroidism being 0 months with a range of 0-3 months. Subclinical hyperthyroidism occurs early due to the radiation damage to the parenchymal cells which causes release of T3 and T4 before late damage occurs which will cause depression of T3 and T4 and elevation of TSH. In a prospective study by Alkan et al[35] to determine thyroid dysfunction after combined therapy for laryngeal cancer, a total of 75 males took part in the study. They studied the incidence of thyroid dysfunction and the alliance between hypothyroidism and variables such as age, type of laryngectomy (partial or total), type of neck dissection (selective or radical) implementation of thyroid lobectomy, tumour stage according to TNM, radiotherapy dose and duration and presence of thyroiditis in surgical specimen. Thyroid hormones were evaluated before treatment, repeated one day before treatment and at two monthly intervals for the first six months and then six monthly

intervals for up to forty-eight months. The average time to detection of hypothyroidism was found to be between 2 and 24 months, 83% of patient developed hypothyroidism within nine months of treatment. Radiotherapy dose, extent of laryngectomy and neck dissection, performance of hemi thyroidectomy and presence of thyroiditis in surgical specimen were found to be risk factors leading to thyroid dysfunction. Age, radiotherapy duration and tumour stage were unrelated to development of hypothyroidism.

Weissler et al[22] in a prospective study of 68 patients evaluated the following variables and their influence on TSH levels, radiotherapy dose, performance of hemi-thyroidectomy, performance of radical neck dissection, gender, hyper-fractionated radiotherapy and use of chemotherapy. They found out that dose of radiotherapy and performance of hemi thyroidectomy was related to development of elevated TSH levels ($p < 0.05$). Performance of radical neck dissection, gender, hyper fractionated radiotherapy and use of chemotherapy were not related to the development of an elevated TSH ($p > 0.05$). Aich et al[21] did a prospective study on 178 patients with one of the aim being to investigate whether neo adjuvant or concurrent chemotherapy has any effect on developing hypothyroidism. From their study chemotherapy was found to have a non-significant effect on the thyroid gland.

Zhixiong et al[36] studied 45 patients with nasopharyngeal carcinoma undergoing external beam radiotherapy to determine radiation induced thyroid gland changes. They found out that an average of 20% thyroid volume reduction occurred in the first six months and further 8% shrinkage at 12 months after radiotherapy. The volume reduction was dependent on mean thyroid radiation doses of between 19-55.6 grays. Serum FT3 and FT4 levels showed mild changes of less than 2.5% at six months, decreased by 8.8% for FT3 and 11.3% for FT4 at twelve months. Hormones became stable at eighteen months where 26% (n=12) had primary hypothyroidism.

3.0 CHAPTER THREE: STUDY JUSTIFICATION AND METHODOLOGY

When treating head and neck cancers with radiotherapy the thyroid gland becomes one of the organs at risk due to close proximity to the area being irradiated. Radiation portals are also directed to the neck especially in cancers with nodal metastasis to the neck and hence expose the thyroid gland to irradiation either directly or by scattered radiation. It has been shown that radiotherapy of head and neck cancer can cause thyroid dysfunction.

Following radiotherapy for head and neck cancers there is no recommended standard follow up with thyroid functions test studies to detect early cases of hypothyroidism or hyperthyroidism which may benefit from early treatment and reduce the co-morbidities associated with head and neck cancers. The study will determine if thyroid hormone profiles are affected by radiotherapy when treating head and neck cancers in our set up. The outcome of the study will help us come up with protocols and guidelines for inclusion of thyroid functions tests as part of follow up for patients following radiotherapy for head and neck cancers. Currently, there are no similar studies which have been done in our set up.

3.1Research Question

What are the pattern and determinants of early thyroid hormone profiles changes following radiotherapy for head and neck cancer at KNH?

3.2 Objectives

3.2.1 Broad Objectives

To determine pattern and determinants of early thyroid hormone profiles changes following radiotherapy for treatment of head and neck cancer patients at Kenyatta National Hospital.

3.2.2 Specific Objectives

a) To determine thyroid hormone profiles in patients with head and neck cancers prior to radiotherapy.

b) To determine thyroid hormone profiles at three months post radiotherapy.

c) To determine factors that affect the thyroid hormone profiles following radiotherapy for treatment of head and neck cancers.

3.3 Research Methodology

3.3.1Study Design

This was a prospective observation study over a duration of 14 months.

3.3.2 Study Area

The study was conducted at the Ear, Nose and Throat department and Cancer Treatment Centre of Kenyatta National Hospital (KNH).

3.3.3 Study Population

The study population included patients scheduled to undergo radiotherapy for treatment of head and neck cancers.

3.3.4 Inclusion Criteria

a) Patients with a histological diagnosis of head and neck cancer and received curative radiotherapy.

b) Patients who received curative chemotherapy with radiotherapy.

c) Post-surgical patients who received curative adjuvant radiotherapy with or without chemotherapy.

d) Patients who were aged eighteen years and above.

e) Patients who consented to the study.

3.3.5 Exclusion Criteria

a) Patients with a known thyroid disease.

b) Patients who had any form of thyroid surgery.

c) Patients who received palliative radiotherapy.

d) Patients who failed to give consent to the study.

3.4 Sample Size Calculation

Sample size calculation for finite population was used

$$n = \frac{Nz^2pq}{E^2(N-1) + z^2pq}$$

n = Desired sample size

N = population size (number of patients scheduled to undergo radiotherapy for treatment of head and neck cancer at Kenyatta National Hospital per month is approximately 20, and for 3 months of the patients recruitment the total will be approximately 60).

Z = value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI)

p = expected true proportion (estimated at 42.2%, from study conducted by Srikantia et al (11)who evaluated 45 patients prospectively over nine months to investigate how common hypothyroidism was after EBRT to the neck in head and neck cancer patients and found out that 42.2 % developed radiation induced hypothyroidism.)

$$q = 1 - p$$

E = desired precision (0.05)

$$n = \frac{60\ x\ 1.96^2\ x\ 0.42x\ 0.58}{0.05^2(60-1) +\ (1.96^2\ x\ 0.42\ x\ 0.58)} = 52$$

Addition of 15% due to loss of follow up,15% of 52=7.8 ~ 8

A sample size of 60 patients was required in this study.

3.5 Procedure

Patients who met the inclusion criteria and gave consent were recruited into the study. Consecutive sampling technique was used to recruit patients into the study. Their bio-data, history, and physical examination were undertaken by the principal investigator. The site and stage of the disease as per TNM staging, histological diagnosis was recorded. TNM staging was done using the reported radiological imaging and the clinical examination findings. The planning treatment volume to the neck and primary tumour in Grays was also recorded. Those patients receiving induction chemotherapy had their drugs of chemotherapy recorded and the number of cycles to be administered. These patients were also followed up to the end of their induction chemotherapy to record the number of cycles given. The day of commencement of radiotherapy for these patients who had induction chemotherapy was also recorded on the data collection tool.

Pre-treatment blood samples was drawn for thyroid functions studies (TSH, FT4, FT3) on the day of commencement of radiotherapy or chemotherapy and analysed at the department of paediatric and child health laboratory of the university of Nairobi using liaison R-chemiluminescence analyser fully automated machine. The normal reference values for the laboratory for FT3 is 2.2-4.2 pg/ml, FT4 is 0.8-1.7ng/dl and TSH is 0.3-3.6 uIu/ml. These reference ranges are derived from the equipment manufacturer. The amount of blood withdrawn was 4mls.Those patients who had deranged thyroid functions were referred accordingly to the endocrinology clinic for follow up. The two machines used for

radiotherapy at Kenyatta National Hospital for head and neck cancer included bhabhatron cobalt unit from India and linear accelerator elekta synergy unit from Canada. The form of radiotherapy delivered by these machines was external beam radiotherapy at a dose of 2.0 Grays per fraction per day for each patient up to a total of 33 fractions. During radiotherapy the spinal cord was shielded off at 44 Grays , the neck was radiated to 50 Grays with a boost of the primary tumour up to 66 Grays in all patients.

Patients were reviewed at the end of radiotherapy to schedule for three-month visit. Blood sample of 4mls was withdrawn again for analysis of thyroid functions at three months. The details of treatment received was captured in the data collection sheet, whether radiotherapy alone, radiotherapy with chemotherapy, surgery with radiotherapy and chemotherapy.

3.6 Data Management and Analysis

All the data was recorded in the data collection sheet and each sheet was coded with the code assigned to each individual patient. The data collection sheets were locked in a cabinet. Upon completion of data collection, the data was entered in google sheet for analysis. Statistical package for social sciences (SPSS) was used in this study. Data was expressed as means and standard deviations and percentages. Means were analysed with one-way analysis of variance (ANOVA) test. Exact fisher test was used to analyse the effects of age, gender, TNM stage, chemotherapy, radiotherapy machine type, duration of treatment effects on development of thyroid dysfunction.

3.7 Quality Control

This was a continuous process throughout the study to ensure that the results are valid and can be replicated. History, physical examination, review of histological report plus the images was carried out by the principal investigator. Blood samples for thyroid functions test was withdrawn by a phlebotomist and put in a plain well labelled vacutainer and analysed at the department of paediatric and child health laboratory at the University of Nairobi.

The machine for analysing thyroid function tests was tested on a daily basis as part of quality control. For precision data each reagent kit has a Quality control (Qc) kit which is run on the machine before using the reagent kit to help generate a graph where the test values should range. The Quality control was run on daily basis. The test results for thyroid function studies for each patient was appropriately entered on the data collection sheet. Cross checking was done for data collected and any inconsistencies noted rectified.

Quality control for radiotherapy machines was done on a daily basis by the operator of the machine and on a weekly and monthly basis by the radiation oncology medical physicist. Radiation checks using phantoms and docimeters was carried out. These radiations related quality control assist in checking side effects on the patients. Calibration of the machines was done on monthly basis to give the dose rate, which is the dose delivered per minute.

3.8 Ethical Consideration

The study was commenced after ethical approval by the KNH-UON ethics and research committee (approval letter P235/03/2019). Recruitment of patients was by consent, the patients received full disclosure of the nature of the study. No extra cost was incurred by the patients. The cost of doing thyroid function studies was catered for by the principle researcher. Patients who declined to be recruited into the study were not discriminated against.

The results of thyroid function studies were shared with the patients and those who were found to have deranged thyroid functions were referred appropriately to the endocrinology clinic for follow up. Confidentiality was maintained by ensuring that bio data was coded and secured under lock and key. At the end of the study the raw data was coded and stored for further study.

3.9 Study Result Dissemination Plan

Result will be submitted to the university in form of a thesis. The findings of the study will also be shared during presentations in meetings, seminars, conferences, journals and other forums. Hard copies of the study will be availed at UoN department of surgery, college of health sciences library and ENT department library. A soft copy will also be available on the university of Nairobi online portal for reference and dissemination. A manuscript will be prepared and submitted for publication in a journal as part of the partial fulfilment of the requirement of the degree of master of medicine in ear nose and throat surgery.

4.0 CHAPTER FOUR: RESULTS

A total of 60 patients were recruited into the present study. This constituted of 37(61.7%) males and 23(38.3%) females. The mean age of patients in years was 52.2 ±16.2 and ranged from 18yrs to 82 years. Majority of patients were between the ages of 41-50 years and 51-60 years at 23.3% (14 patients) each respectively as shown in the figure 1 below;

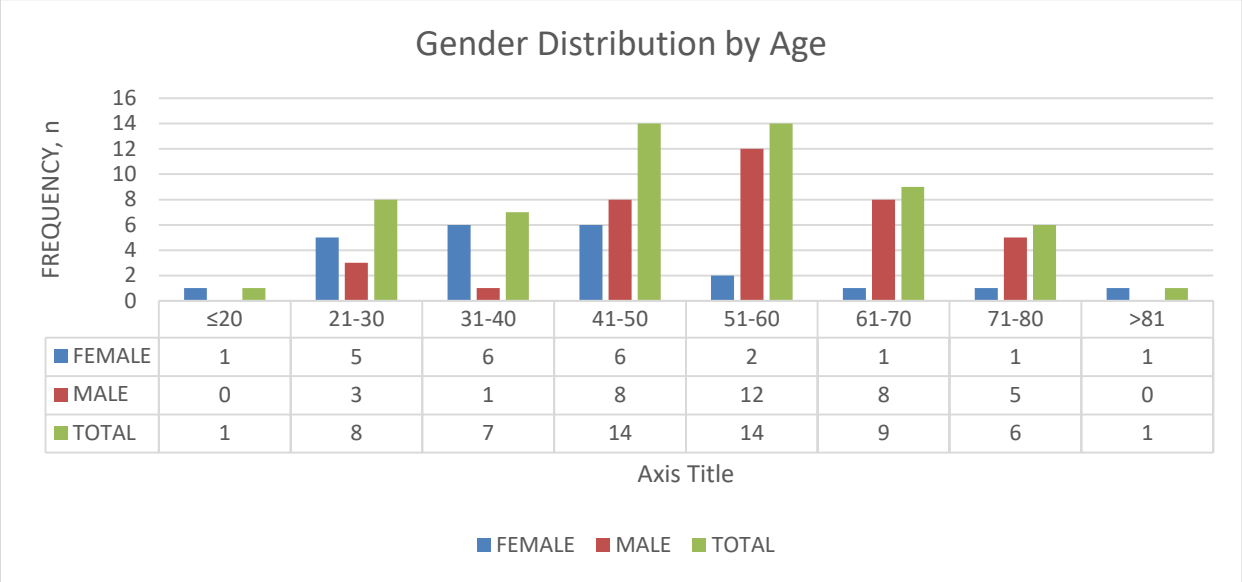

Figure 1: Age gender distribution

A total of 10 patients were lost to follow up and the results presented subsequently include results of 50 patients who completed the study.

4.1 Cancer Characteristics

4.1.1 Cancer Subsites

Majority of our patients had oral cavity cancer at 34% and laryngeal cancers at 28% as depicted in figure 2 below.

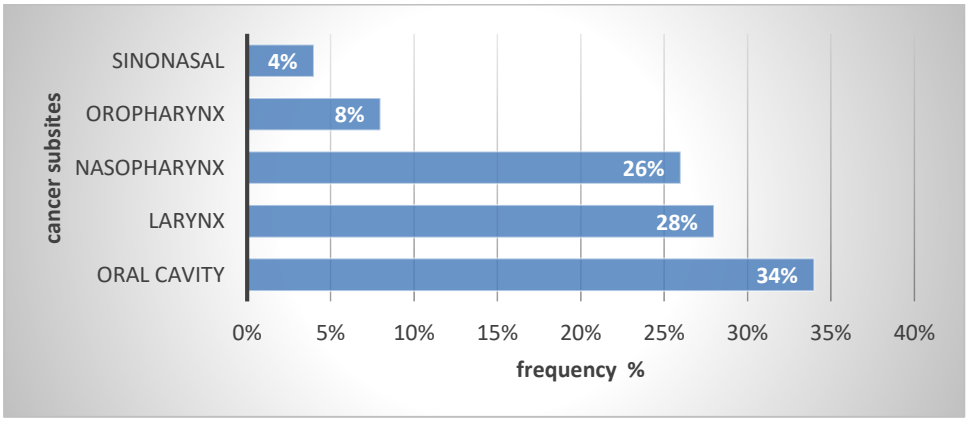

Figure 2: Cancer Subsites

4.1.2 Tumour Node Metastases staging

T1 and T2 tumours were relatively rare at 16%, most patients had T3 and T4 tumours at 84% at the time of recruitment. Cervical nodal metastasis N2 and N3 was found in 76% of patients. Distant metastasis was only in 2(4%) patients as depicted in table 1 below.

Table 1: Tumour node metastases stage

	Characteristics	frequency	%
T-stage	T1	2	4.0
	T2	6	12.0
	T3	13	26.0
	T4	29	58.0
N-stage	N0	6	12.0
	N1	6	12.0
	N2	19	38.0
	N3	19	38.0
M-stage	M0	48	96.0
	M1	2	4.0

4.1.3 Histological Characteristics

Patients with Well differentiated cancers were the majority at 52% as depicted in figure 3 below;

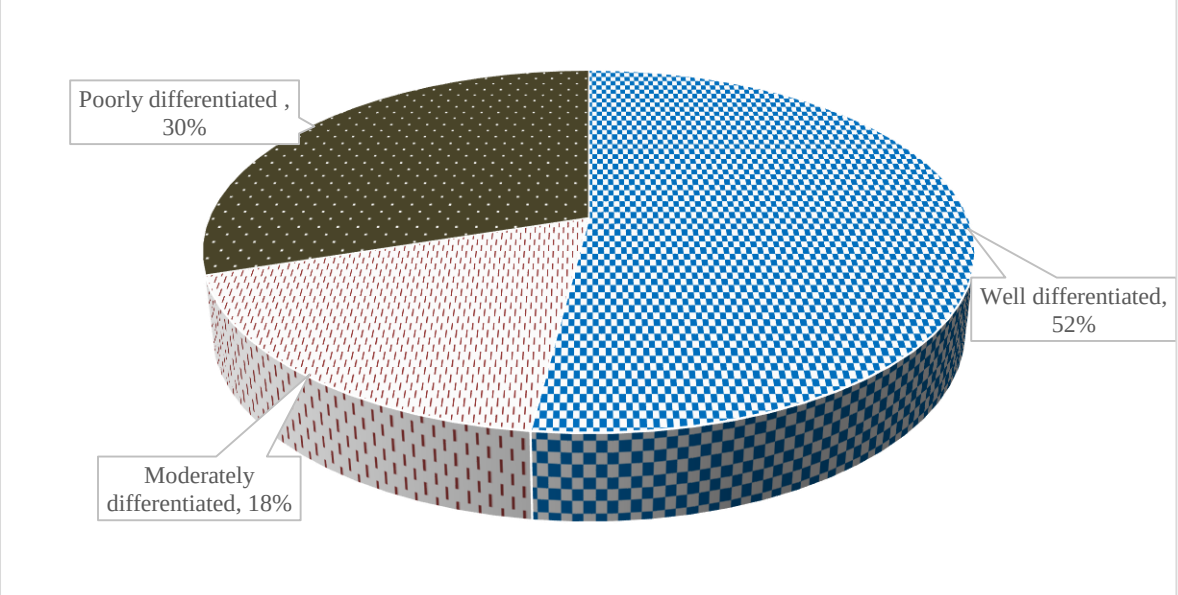

Figure 3:Histological characteristics

4.2 Treatment Modalities

Patients were treated with both Cobalt-60 and linear accelerator (LINAC) radiotherapy machines in almost equal measure at a rate of 52% and 48 % respectively, the mean radiotherapy treatment duration was 56.1±51.8 days. Majority of patients received both radiotherapy and chemotherapy (40 patients) which represent 80%. Only 10 (20%) patients received radiotherapy alone. The chemotherapy given and the number of cycles is as shown in table 2 below.

Table 2:Treatment Modalities

	Characteristic	**Frequency**	**%**
Radiotherapy machine	COBALT-60	26	52.0
	LINAC	24	48.0
Duration of treatment	Mean ±SD	56.1days±51.8days	
Chemotherapy	Yes	40	80.0
	No	10	20.0
Chemotherapy drugs	Cisplatin	26	52.0
	Cisplatin, Docetaxel, 5-FU	14	28.0
Chemotherapy cycles	One	2	4.0
	Two	2	4.0
	Three	36	72.0

4.3 The Changes in Thyroid Function during the Study Period

There was a statistical significance difference between mean pre radiotherapy FT3 (2.94± 0.72 and three month post radiotherapy FT3 (2.96± 0.84) with a p value of 0.04 . There was an increase in mean pre radiotherapy FT4 from 1.11±0.40 to 1.15±0.43. TSH means also increased from 2.14±3.00 to 4.71±9.50. Using analysis of variance there was no statistical significant difference between mean pre radiotherapy FT4 and TSH with a p value of 0.66 and 0.07 respectively as depicted in table 3 below.

Table 3: Mean thyroid functions before and after radiotherapy

Thyroid function test	**Before radiotherapy**	**After radiotherapy**	**Significance(P-value)**
FT3	2.94±0.72	2.96±0.84	**0.04**
FT4	1.11±0.40	1.15±0.43	0.66
TSH	2.14±3.00	4.71±9.50	0.07

4.5 Thyroid Dysfunction Before and After Radiotherapy

Thyroid dysfunction was present in 2(4%) patients before commencement of radiotherapy and at the end of three months post radiotherapy, 15 (30%) patients had at least some form of

thyroid dysfunction. Prevalence of thyroid dysfunction was compared between start and three months post radiotherapy. Findings are presented in the table 4 below;

Table 4: Thyroid dysfunction before and after radiotherapy

Type of Dysfunction	**Before Radiotherapy**	**3-Months post radiotherapy**	**Significance(ANOVA)**
Normal thyroid Function	48(96%)	35(70%)	**<0.001**
Subclinical hypothyroidism	1(2%)	6(12%)	**0.05**
Clinical Hypothyroidism	00	6(12%)	**0.01**
Subclinical Hyperthyroidism	1(2%)	1(2%)	1.00
Clinical hyperthyroidism	00	2(4%)	0.16

4.6 Factors Affecting Development of Thyroid Dysfunction

Factors that were found to affect development of thyroid dysfunction included degree of differentiation of the tumour and chemotherapy. Patients with well differentiated tumours were found to have higher incidences of thyroid dysfunction at three months compared to poorly differentiated tumours with a p value of <0.04. Those patients who received chemotherapy and radiotherapy were found to have higher incidences of thyroid dysfunction compared to those who received radiotherapy alone with a p value of <0.03 as depicted in table 5 below.

Table 5: Factors affecting development of thyroid dysfunction

Factors		**Thyroid dysfunction**		**Total**	**P-value(Fishers exact)**
		No	**Yes**		
Gender	Female	12(63.2)	7(32.8)	19	
	Male	23(74.2)	8(25.8)	31	0.53
Age	≤20	1(100)	00	1	0.12
	21-30	5(83.3)	1(16.7)	6	
	31-40	2(40)	3(60)	5	
	41-50	9(75)	3(25)	12	
	51-60	8(80)	2(20)	10	
	61-70	4(44.4)	5(55.6)	9	
	71-80	6(100)	00	6	
	>81	00	1(100)	1	
Cancer sub-site	Larynx	9(64.3)	5(35.7)	14	0.08
	Oropharynx	3(75.0)	1(25.0)	4	
	Nasopharynx	12(92.3)	1(7.4)	1	
	Sino nasal	0	2(100)	2	
	Oral cavity	11(64.7)	06(35.3)	17	
T-stage	T1	2(100)	0	2	0.09
	T2	5(83.3)	1(16.7)	6	
	T3	8(61.5)	5(38.5)	13	
	T4	20(69.0)	9(31.0)	29	
N-stage	N0	2(33.3)	4(66.7)	6	
	N1	5(83.3)	1(16.7)	6	
	N2	12(63.2)	7(36.8)	19	
	N3	16(84.2)	3(16.8)	19	
M-stage	M0	35(72.9)	13(27.1)	48	0.09
	M1	00	2(100)	2	
Differentiation	Well differentiated	15(57.7)	11(42.3)	26	**0.04**
	Moderately differentiated	6(66.7)	3(33.3)	9	
	Poorly differentiated	14(93.3)	1(6.7)	15	
Radiotherapy machine	COBALT-60	16(71.5)	10(38.5)	26	0.22
	LINAC	19(79.2)	05(20.8)	24	
Duration of radiotherapy	Mean ±SD	60.0±61.7 n=35	47.0±5.8 n=15	50	0.42
Chemotherapy	Yes	27(67.5)	13(32.5)	40	**0.03**
	No	8(80)	2(20)	10	
Chemotherapy drugs	Cisplatin	14(53.8)	12(46.2)	26	
	Cisplatin, Docetaxel, 5-FU	13(92.9)	01(7.1)	14	
Chemotherapy cycles	None	8(80)	2(20)	10	0.70
	One	1(50)	1(50)	2	
	Two	2(100)	0	2	
	Three	24(66.7)	12(33.3)	46	

5.0 CHAPTER FIVE: DISCUSSION, CONCLUSION & RECOMMENDATIONS

5.1 Discussion

One of the side effects of treatment of head and neck cancers with radiotherapy or chemo-radiotherapy include damage to the thyroid gland. Damage can be divided into acute, sub-acute and late injuries. Acute injuries occur within three months, subacute from three months to one year and late injuries occur after one year.

In our study we have found a significant increase in mean values of FT3 from pre-treatment mean values of 2.94± 0.72 to 2.96± 0.84 at three months. This increase was statistically significant with a p value of 0.04. Similarly FT4 increased from pre-treatment mean values of 1.11± 0.04 to 1.15± 0.43 which was not statistically significant with a p value of 0.66. The increase in FT3 and FT4 in our study could be attributed to the radiation damage to thyroid gland parenchymal cells which causes release of FT3 and FT4 before late damage occurs which causes depression of FT3 and FT4 and elevation of TSH. Our study contrasts the findings of Madhani et al [33] and Chougule et al [34] who found mean values of FT3 and FT4 to statistically decrease at the third month of follow up. The mean TSH in the current study also increased from 2.14± 3 to 4.71± 9.50 which was not statistically significant with a p value of 0.07. This increase in mean TSH could be attributed to the normal physiological response mechanisms that the anterior pituitary gland responds with in situations of fluctuating free thyroid hormones levels (FT3 and FT4) in circulation. Increase in the mean values of TSH in our study is similar to findings of Madhani et al[33] who found TSH to increase but within the reference ranges. However, in the Chougule et al [34] study the mean values of TSH did not change.

At commencement of treatment with radiotherapy or chemo-radiotherapy only two patients were found to have thyroid dysfunction that is one patient with subclinical hypothyroidism and one patient with subclinical hyperthyroidism. This constituted 4% of the population under investigation. The patient who had subclinical hypothyroidism in our study progressed to clinically overt hypothyroidism while the one who had subclinical hyperthyroidism progressed to hyperthyroidism at three months. It is therefore important to identify patients with subclinical thyroid dysfunctions before commencement of treatment because they are likely to convert to clinically overt disease after treatment.

Three months after completion of radiotherapy 30% of our patients had some form of thyroid dysfunction which was statistically significant compared to before radiotherapy with a p

value of <0.001. Six (12%) of the patients had subclinical hypothyroidism and 6(12%) had clinical hypothyroidism. This was statistically significant with a p value of 0.05 and 0.01 respectively. One (2%) patient developed subclinical hyperthyroidism while 2 (4%) patients developed clinical hyperthyroidism. This was however not statistically significant. Our figures at three months are higher for development of hypothyroidism if compared to Vivek et al [38] who only had a figure of 2.43% at three months and 19.51% at nine months. The low figures in Vivek et al[38] could be due to the fact that in their study patients were radiated using three-dimension linear accelerator while in our study we had our patients radiated using linear accelerator (24 patients) and Cobalt-60 machine (26 patients). The linear accelerator radiotherapy machine is able to conform radiotherapy beams to the target tumour while sparing the surrounding tissues unlike the cobalt 60 radiotherapy machine. In addition patients who had deranged thyroid function test were also excluded from their study unlike in our study where they were included. Our study had almost similar findings to Mehmet et al [32] who had a figure of 14% with subclinical hypothyroidism and 10% with hyperthyroidism although patients were evaluated immediately after completion of radiotherapy with no follow up. Patients in this study were radiated using tele cobalt radiotherapy machine like in our study.

The following variables were evaluated and their influence on development of thyroid dysfunction in our study, gender, age, cancer sub-site, TNM stage, degree of differentiation of the tumour, type of radiotherapy machine, chemotherapy use with radiotherapy, radiotherapy only, and duration of radiotherapy. The degree of differentiation of the tumour was found to influence on development of thyroid dysfunction as patients with tumours which were well differentiated and moderately differentiated developed thyroid dysfunction compared to patients with poorly differentiated tumours with a p value of 0.04. This is in contrast to Chougule et al [34] who found thyroid dysfunction to be more common in poorly differentiated cancers. The difference between our study and chougule et al could be due to the fact that majority of our patients had oral cavity cancers (34%) and laryngeal cancers (28%) and cancers in these locations tend to be more differentiated histologically. In addition majority of the patients in our study had well differentiated cancers at 52% and moderately differentiated at 18% with 30% having poorly differentiated cancers. The finding of more thyroid dysfunction among the more differentiated tumours may not have a scientific backing except that these formed majority of subjects.

Chemotherapy use was found to influence development of thyroid dysfunction in our study with a p value of 0.05 unlike in other studies by Weissler et al [23] and Aich et al [22] who

found chemotherapy not to have any effect on development of thyroid dysfunction. In our study 80% of the patients were treated with both chemotherapy and radiotherapy with only 10% receiving radiotherapy alone. Concurrent use of chemotherapy with radiotherapy is expected to increase radio sensitivity of thyroid gland and increase the incidences of thyroid dysfunction as witnessed in our study.

Majority of our patients were males at 31(62%) whereas females were 19(38%). Head and neck cancers is more common in males in Kenya compared to females as per GLOBOCAN data of 2020[5]. Thyroid dysfunction was found to occur in almost equal measure between males and females. Seven females (32.8%) and 8 males (25.8%) developed thyroid dysfunction with a p value of 0.53 which was not statistically significant. Our findings are similar to those of Capoglu et al [(12)] where gender was found not to influence development of thyroid dysfunction. Other studies have found hypothyroidism to occur more in females compared to males and attributed this to small thyroid volume in females.[24,35]

Majority of our patients were in the age range of 41-50 years and 51-60 years at 24% and 20% respectively. Age was found not to influence development of thyroid dysfunction in our study as dysfunction was distributed across the various age groups with a p value of 0.12. These findings are similar to those by Capoglu et al [(12)] and Alkan et al. [(36)] However, Srinkatia et al [(35)] found age to be a contributor to development of thyroid dysfunction. The elderly were found to develop thyroid dysfunction compared to the young.

In terms of TNM staging T3 and T4 tumours comprised the majority of our patients at 84% and N2 and N3 tumour stage comprised 76%. This late presentation has previously been investigated in our set up by Onyango et al[39] and found to be due to delay in diagnosis and referral from the primary health care facility. The commonest cancers in our study were found to arise from the oral cavity at 34% followed by laryngeal carcinomas at 28%. Vivek et al[38] also had majority of the cancers arising from oral cavity (47.56%) and larynx (23.17%) in their study. When both cancer sub-site and TNM staging were evaluated they were found not to influence development of thyroid dysfunctions with p value of 0.08 and 0.09 respectively. Our study mirrors that of Alkan et al[36] who found cancer subsite and TNM stage not to influence development of thyroid dysfunction.

The type of Radiotherapy machine used had no influence on development of thyroid dysfunction with p value of 0.22. However, 10 patients who developed thyroid dysfunction were irradiated with cobalt-60 machine compared to 5 patients who were radiated with linear accelerator. This could be due to the fact that the linear accelerator radiotherapy machine has capability of conforming radiotherapy to target tumour while sparing adjacent tissues and

organs which cobalt 60 machine lacks. Duration of radiotherapy did not influence development of thyroid dysfunction in the present study (p value 0.42), the mean duration in days for patients who developed thyroid dysfunction was 47.0±5.8 while those who did not had a mean duration of 60.0±61.7. Our findings are similar to those by Alkan et al who found radiotherapy duration not to influence development of thyroid dysfunction.

5.2 Conclusion

The thyroid gland is affected by radiation during treatment of head and neck cancers and the effect can occur early or late. In our study we have found a statistical significant increase in mean values of FT3 and a non-statistical significant increase in mean values of FT4 and TSH at three months. In addition, we have found 30% of the cases developing thyroid dysfunction at three months. Factors that were found to influence development of thyroid dysfunction included chemotherapy and degree of differentiation of the tumour.

5.3 Recommendations

Thyroid hormones monitoring following radiotherapy for head and neck cancers should incorporate part of follow up of these patients especially those patients who receive chemotherapy with radiotherapy and those with well differentiated tumours. This will enable detection of early changes that can be treated and decrease the disease morbidity associated with head and neck cancers. Further studies can be done with a larger cohort and be followed up for longer time to establish the incidences of development of thyroid dysfunction. In addition a larger case control study can also be done to compare radiotherapy on one arm and chemo-radiotherapy on the other arm since majority of our cases received chemoradiotherapy.

5.4 Limitations

Some of the limitations experienced included loss of follow up of patients.

BIBLIOGRAPHY

1. Alistair B, Peter E, Snehal P,et al.Head and neck malignancy: An overview. Principles and practice of head and neck surgery and oncology. 2nd . United kingdom: informa health care;2009.3-6p.

2. Ferlay J, Colombet M, Soerjomataram I, et al. Global and regional estimates of the incidence and mortality of 38 cancers: GLOBOCAN 2018.Lyon:International agency for research on cancer/ World Health Organisation;2018.

3 www.health.go.ke/Kenya national cancer treatment protocols.

4. Deschler DG,Moore MG,Smith RV,eds.Quick reference guide to TNM staging of head and neck cancers and neck dissection classification,5th ed.Alexandria,VA:American academy of otolaryngology-head and neck surgery foundation.2018

5. https://gco.iarc.fr/Kenya

6. Bangalore M, Matthews S, Suntharalingam M, et al. Recent advances in radiation therapy for head and neck cancer. J Oto-Rhino-Laryngol Its Relat Spec. 2007;69(1):1–12.

7. Rieger JM, Zalmanowitz JG, Wolfaardt JF, et al. Functional outcomes after organ preservation treatment in head and neck cancer: a critical review of the literature. Int J Oral Maxillofac Surg. 2006 ;35(7):581–587.

8. Aron Poportzer, Avraham Eisbruch.Radiotherapy for head and neck cancers:radiation physics,radiobiology and general principles. Cumming's otolaryngology head and neck surgery. 5th ed. Mosby Elsevier; 1042 p.

9. Chummy S Sinnatamy. Head and Neck and Spine. Timothy H(ed). Last's anatomy regional and applied. 12th ed. Edinburg: Churchill livingstone elsevier; 2011. 339–340 p.

10. Kim E, Susan M, Scott B, et al.The Thyroid gland. Ganong's review of medical physiology. 24th ed. Singapore: McGraw Hill; 2012. 339–349 p.

11. Emami B, Lyman J, Brown A, Coia L, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys. 1991;21(1):109–122.

12. Koc M, Capoglu I. Thyroid dysfunction in patients treated with radiotherapy for neck. Am J Clin Oncol. 2009 ;32(2):150–153.

13. Nishiyama K, Kozuka T, Higashihara T, et al. Acute radiation thyroiditis. Int J Radiat Oncol Biol Phys. 1996 ;36(5):1221–1224.

14. Nishiyama K, Tanaka E, Tarui Y, et al. A prospective analysis of subacute thyroid dysfunction after neck irradiation. Int JRadiat Oncol Biol Phys. 1996;34(2):439–444.

15. Jereczek-Fossa BA, Alterio D, Jassem J, et al. Radiotherapy-induced thyroid disorders. Cancer Treat Rev. 2004;30(4):369–384.

16. CR C. Hypothyroidism in head and neck cancer patients: experimental and clinical observations. Laryngoscope 1994;104:1-21.

17. Feehs RS, McGuirt WF, Bond MG, et al. Irradiation: A Significant Risk Factor for Carotid Atherosclerosis. Arch Otolaryngol Neck Surg. 1991 ;117(10):1135–1137.

18. DeGroot LJ. Radiation and thyroid disease. Baillieres Clin Endocrinol Metab. 1988 ;2(3):777–791.

19. Williams ED. TSH and thyroid cancer. Horm Metab Res Suppl Ser. 1990;23:72–75.

20. Bakhshandeh M, Hashemi B, Mahdavi SR, et al. Evaluation of Thyroid Disorders During Head-and-Neck Radiotherapy by Using Functional Analysis and Ultrasonography. Int J Radiat Oncol Biol Phys. 2012 ;83(1):198–203.

21. Sinard RJ, Tobin EJ, Mazzaferri EL, et al. Hypothyroidism after treatment for nonthyroid head and neck cancer. Arch Otolaryngol Head Neck Surg. 2000 ;126(5):652–657.

22. Aich RK, Ranjan DA, Pal S, et al. Iatrogenc hypothyroidism: a consequence of external beam radiotherapy to the head & neck malignancies. J Cancer Res Ther. ;1(3):142–146.

23. Weissler MC, Berry BW. Thyroid-stimulating hormone levels after radiotherapy and combined therapy for head and neck cancer. Head Neck. 1991 ;13(5):420–423.

24. Alterio D, Jereczek-Fossa BA, Franchi B, et al. Thyroid disorders in patients treated with radiotherapy for head-and-neck cancer: a retrospective analysis of seventy-three patients. Int J Radiat Oncol Biol Phys. 2007 ;67(1):144–150.

25. Gaitonde DY, Rowley KD, Sweeney LB et al. Hypothyroidism: An Update. Am Fam Physician. 2012;86(3):244–251.

26. Safer JD. Thyroid Hormone and Wound Healing. J Thyroid Res .2013

27. Kravets I. Hyperthyroidism: Diagnosis and Treatment. Am Fam Physician. 2016 ;93(5):363–370.

28. Garcia-serra A, Amdur RJ, Morris CG, et al. Thyroid Function Should Be Monitored Following Radiotherapy to the Low Neck. Am J Clin Oncol. 2005;28(3):255–258.

29. Tell R, Lundell G, Nilsson B, et al. Long-term incidence of hypothyroidism after radiotherapy in patients with head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2004 ;60(2):395–400.

30. Karmisholt J, Andersen S, Laurberg P, et al. Analytical goals for thyroid function tests when monitoring patients with untreated subclinical hypothyroidism. Scand J Clin Lab Invest. 2010 ;70(4):264–268.

31. Andersen S, Bruun NH, Pedersen KM, et al. Biologic variation is important for interpretation of thyroid function tests. J Am Thyroid Assoc. 2003;13(11):1069–1078.

32. Koc M, Unuvar N, Sen RC, et al. A prospective evaluation of early thyroid dysfunction on completion of neck radiotherapy. Oral Oncol. 2003;39(6):597–600.

33. Madhani N, Saini SK, Srivastava S,et al. Acute Thyroid Profile Changes During External Beam Irradiation of Neck. Indian J Otolaryngol Head Neck Surg. 2017; 1157-1167

34. Chougule A, Kochar B. Thyroid dysfunction following therapeutic external radiation to head and neck cancer. Asian Pac J Cancer Prev .2011;12(2):443–445.

35. Srikantia N, Rishi KS, Janaki MG, et al. How common is hypothyroidism after external radiotherapy to neck in head and neck cancer patients? Indian J Med Paediatr Oncol Off J Indian Soc Med Paediatr Oncol. 2011;32(3):143–148.

36. Alkan S, Baylancicek S, Çiftçic M, et al. Thyroid Dysfunction after Combined therapy for Laryngeal Cancer: A Prospective Study. Otolaryngol Neck Surg. 2008 ;139(6):787–791.

37. Lin Z, Wu VW-C, Lin J, et al. A Longitudinal Study on the Radiation-Induced Thyroid Gland Changes After External Beam Radiotherapy of Nasopharyngeal Carcinoma. Thyroid. 2010 ;21(1):19–23.

38.Vivek I,Sachdeva J,Singh N et al. Evaluation of thyroidal dysfunction in patients with head and neck cancer receiving radiation therapy or chemoradiation. J.evolution med.dent sci 2019;8(42):3155-3160.

39. Onyango JF,Macharia IM.Delays in diagnosis,referral and management of head and neck cancer presenting at Kenyatta national hospital,Nairobi.East Africa medical journal 2006;83(4):85-91.

BUDGET

Core Activity	Cost (ksh)
Thyroid function test @1500	165000
Stationary	10000
Stastician	30000
Research assistant	40000
Miscellaneous	20000
Total	265 000

TIME FRAME

Activity	Sept-Dec 2018	March-August 2019	August 2019-Oct 2020	Nov-Dec 2020	Jan - March 2021	April-August 2021
Research proposal and presentation						
Ethical clearance						
Data collection						
Data entry and analysis						
Presentation of results						
Submission for marking and publication						

APPENDICES

Appendix I: Consent Form (English)

1. Introduction

This informed consent form will be administered by the principal investigator to patients presenting to KNH with head and neck cancer and scheduled to receive radiotherapy. We are requesting these participants to participate in this study entitled **'Patterns and determinants of early thyroid hormone profile changes following radiotherapy for head and neck cancers at Kenyatta National Hospital.**

Principal investigator:

- Dr Thomas Muthii Mureithi, school of medicine, department of surgery, university of Nairobi.

Supervisors: Dr John Ayugi, Dr Sophie Gitonga, Dr Catherine Nyongesa

This informed consent has two parts:

- Information sheet(to share information about the research with you)
- Certificate of consent(for signature if you agree to take part)

You will be given a copy of the full informed consent form

Part one: information sheet

Introduction

I am Dr Thomas Muthii Mureithi, a master student at the University of Nairobi. I am conducting a research on **'patterns and determinants of early thyroid hormone profile changes following radiotherapy for head and neck cancers at Kenyatta national hospital'.** Information will be given to you and you may feel free to ask questions before participating in the research. There may be some words that you don't understand, please ask me to explain as we go through the information. If you have questions later, you can ask them my contacts are available on this consent form.

Purpose of the research

Thyroid dysfunction following radiotherapy is a common complication, if UN recognised can increase the morbidity associated with head and neck cancers. The purpose of this research is to investigate the patterns and determinants of early thyroid hormone profile changes following radiotherapy for head and neck cancers.

Risks

The study poses no risk to the participants except for the slight pain you will feel while blood is being withdrawn from you.

Benefit

This study will improve patient management following radiotherapy for head and neck cancers, those patients who will be found to have any form of thyroid function tests derangements will benefit from timely referral and management. There are no financial benefits in participating in the study.

Participant selection

We invite all patients with head and neck cancers scheduled for radiotherapy at Kenyatta National Hospital to participate in the study.

Voluntary participation

Your participation in this research is entirely voluntary. No compensation or remuneration will be offered to the participant of the study. Whether you choose to participate or not all the services you receive at this hospital will continue and nothing will change. If you choose to participate in this research project no extra cost will be incurred.

Procedure and protocol

Description of the process

Once consented, I will ask you regarding your current complaints and past medical history. I will carry out a complete Ear, Nose, Throat, Head and Neck examination, after which blood sample of around 4mls will be withdrawn from you for analysis of thyroid function tests before you start your radiotherapy sessions. Three months after you have completed your radiotherapy we will review you and repeat the blood test to assess whether radiotherapy affected your thyroid gland. A copy of both test results will be availed to you.

Confidentiality

This research will improve follow up and management of patient with head and neck cancers following radiotherapy. We will not share the identity of those participating in this research. The information that we collect from this research will be kept confidential. Information about you will only be able to be visualized by the researchers. Any information about you will have a research number instead of your name on it. Only the researchers will know what your number is and we will lock that information up.

Right of withdrawal

If at any point you feel you don't want to continue participating, you have the right to withdraw your participation. This will not alter the treatment you were normally supposed to receive.

Sharing the results

Results of this study will be made available to the department of surgery of the University of Nairobi, college of health sciences library. The study will also be published online for access to anyone who might require them.

Contacts

In case you want to contact us for any reason you may use the contact below.

Principal researcher:

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Resident in ENT, Head and Neck surgery,

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Phone : 0722867302

Dr. Catherine Nyongesa

Consultant oncologist

Kenyatta National Hospital

Email: catherinenyongesa@yahoo.com

Phone:0723698888

If you have any questions on your rights as a participant contact the *Kenyatta National Hospital/UON- Ethics and Research Committee (KNH/UON-ERC)* by calling *2726300 Ext. 44355*.

PART II: Certificate of Consent **Serial Number: _____**

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it .Questions that I have asked have been answered to my satisfaction. I _____ consent voluntarily to participate as a participant in this research.

Name of Participant_____ Signature of Participant _____

Researcher: Dr Thomas Muthii Mureithi Signature _____

Date _____

Appendix II: Consent Form (Swahili)

Kiambatisho-1: Fomu ya Ridhaa yaTaarifa

Fomu hii ya idhini ya ruhusa itasimamiwa na mchunguzi mkuu kwa wagonjwa wanaofika hospitali kuu ya Kenyatta na saratani ya kichwa na shingo ambao wameratibiwa kutibiwa kutumia miale. Tunawaomba washiriki hawa kushiriki katika utafiti huu utakao angalia dalili za mapema za ubadilifu wa tezi homoni baada ya kutumia miale kutibu saratani ya kichwa na shingo

Mtafiti Mkuu:

- Daktari Thomas Muthii Mureithi, shule ya udaktari, idara ya upasuaji, chuo kikuu cha Nairobi.

Wasimamizi: Daktari John Ayugi, Daktari Sophie Gitonga, Daktari Catherine Nyongesa

Hii fomu ina sehemu mbili;

• Karatasi ya habari (kushiriki habari kuhusu utafiti na wewe)

• Hati ya idhini (kwa ishara ikiwa unakubali kushiriki)

Utapewa nakala ya fomu kamili ya idhini.

A. Sehemu ya Kwanza: Karatasi ya Habari

Utangulizi

Jina langu ni Daktari Thomas Muthii Mureithi, mwanafunzi wa shahada katika Chuo Kikuu cha Nairobi. Ninafanya utafiti kuangalia dalili za mapema za ubadilifu wa tezi homoni baada ya kutumia miale kutibu saratani ya kichwa na shingo.

Nia ya uchunguzi

Ubadalifu wa tezi homoni baada ya kutumia miale kutibu saratani ya shingo na kichwa ni moja wapo ya madhara. Huu ubadilifu ukikosa kujulikana unaweza sababisha madhara kwa wagojwa wanaougua saratani ya shingo na kichwa. Nia ya uchunguzi huu nikuangalia jinsi ubadilifu unafanyika pamoja na vile vitu zinasababisha ubadilifu huo.

Hatari

Hakuna hatari yoyote itakayotarajiwa utakaposhiriki utafiti huu ilatu uchungu kidogo utakapo ndugwa shindano kutoa damu.

Faida ya utafiti

Utafiti huu utasaidia kuboresha usimamizi wa wagonjwa wanaougua saratani ya kichwa na shingo baada ya kutumia miale Kama njia ya matibabu. Hakuna manufaa yakifedha itatolewa kwa kushiriki utafiti huu.

Waanao alikwa kujihusisha na utafiti

Mtafiti ana wakaribisha wagonjwa wote wanaougua saratani ya kichwa na shingo ambao wameratibiwa kutibiwa kutumia miale kushiriki katika utafiti huu katika Hospitali ya Taifa ya Kenyatta .

Kushiriki

Kushiriki utafiti huu utakuwa kwa njia ya kujitolea na kwa hivyo hakuna malipo yoyote atakayolipwa mshiriki wa utafiti huu. Iwapo hungependa kushiriki ,uamuzi huu hautakuathiri kwa njia yoyote iwe matibabu yako au utakavyo hudumiwa.

Maelezo kuhusu mchakato

Iwapo utakubali kushiriki utaulizwa maswali machache kuhusu malalamiko yako ya sasa na historia ya haliyako. Nitapima hali ya ugonjwa wako wa kichwa na shingo.Nitatoa damu ili tupime kiwango cha tezi homoni kwa mwili kabla uanze kutibiwa na miale. kiwango cha damu ambacho kitatolewa ni cha chini mno milliter nne pekee. Baada ya kumaliza matibabu kwa kuchomwa na miale tutarudia kipimo cha damu baada ya miezi tatu kuangalia kama kuna ubadilifu wa tezi homoni. Utatambulishwa kuhusu uchunguzi na umuhimu wa matokeo.

Usiri

Maelezo unayoyatoa juu

Yako mwenyewe itahifadhiwa kwa siri na itatumika tu kwa madhumuni ya utafiti huu. Zaidi ya haya nambari za utafiti zitatumika badala ya majina kutambulisha washirika wa utafiti.

Haki ya kujitoa kwa utafiti

Kushiriki utafiti huu ni kwa kujitolea na iwapo hungependa kushiriki, uamuzi wako utaheshimiwa na pia hautathiri kwa njia yoyote matibabu yako. Bali utaendelea kupokea matibabu na huduma ya hospitali hii kama hapo awali.

Kushiriki Matokeo

Matokeo ya utafiti huu yatapatikana kwa idara ya upasuaji wa Chuo Kikuu cha Nairobi, maktaba ya chuo cha ubora wa afya wa binadamu chuoni kikuu cha Nairobi, hospitali ya kitaifa ya Kenyatta. Matokeo ya utafiti pia yatachapishwa mtandaoni kwa upatikanaji kwa mtu yeyote anayeweza kuhitaji.

Mawasiliano

Mtafiti mkuu

Daktari Thomas Muthii Mureithi, mwanafunzi wa upasuaji wa masikio,pua na koo,

Chuo kikuu cha Nairobi,

Nambari ya simu: 0723470406

Baruapepe: muthiithomas@gmail.com

Wasimamizi:

Daktari John Ayugi

Daktari wa upasuaji wa masikio,pua na koo

Idara ya upasuaji, kitengo cha upasuaji.

Chuo kikuu cha Nairobi,

Nambari ya simu: 0722883041

Baruapepe: johnayugi@gmail.com

Daktari Sophie Gitonga

Daktari wa upasuaji wa Masikio,pua na koo

Hosipitali kuu ya Kenyatta,

Nambari ya simu: 0722867302

Baruapepe: sereyans@gmail.com

Daktari Catherine Nyongesa

Daktari wa saratani

Hospitali kuu ya Kenyatta

Nambari ya simu: 0723698888

Baruapepe: catherinenyongesa@yahoo.com

Maswali kuhusu haki yako ya kujiunga na utafiti yana weza kutumwa kwa *Kenyatta National Hospital/UON- Ethics and Research Committee (KNH/UON-ERC)* kwa nambari *2726300 Ext. 44355*.Mwenyekiti

SehemuYa II: Shahada ya Idhini

Nambari Maalum:_____

Nimesoma maaelezo yote ya utafiti huu au nime somewa maaelezo haya na nimekuwa na fursa ya kuuliza maswali .Maswali yangu yamejibiwa kadri na matarajio yangu kwa njia ya kuridhisha.Kwa hivyo ningependa kupeana idhini yangu na pia kujitolea kushiriki kwa utafiti huu .

Jina lamshiriki: _____ Sahihi la mshiriki:_____

Mtafiti mkuu: Dkt Thomas muthii mureithi Sahihi ya mtafiti mkuu: _____

Tarehe: _____ Tarehe: _____

Appendix III: Data Collection Form

Study number.....

a) Demographics

Age..... Gender.....

b) Cancer

Cancer site.....

TNM staging .....

Histological type and grade.....

c) Radiotherapy

Machine type.....

Dosage of DXT to neck……

Dosage to primary.....

Duration.....

Start date.....

Completion date.....

d) Chemotherapy

Name of chemotherapy drugs given

i. .....
ii. .....
iii. .....
iv. .....

Number of cycles .....

e) Surgery

Type of surgery.....

f) Complications

i. .....
ii. .....
iii. .....
iv. .....

g) Thyroid functions results

	Pre radiotherapy	3 months Post radiotherapy	Normal reference ranges
TSH			
FT3			
FT4			

Appendix IV: KNH/UoN-ERC Letter of Approval

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref. No.KNH/ERC/R/170

2nd October 2020

Dr. Thomas Muthii Mureithi
Reg. No.H58/82360/2015
Dept. of Surgery
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Mureithi

Re: Approval of Annual Renewal – study titled 'Patterns and Determinant s of Early Thyroid Hormone Profile changes following Radiotherapy for head and Neck Cancer at Kenyatta National Hospital' (P235/03/2019)

Refer to your communication dated September 21, 2020.

This is to acknowledge receipt of the study progress report and hereby grant annual extension of approval for ethical research protocol P235/03/2019.

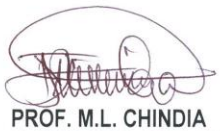
The approval dates are 8th August 2020 – 7th August 2021.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH- UoN ERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH- UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH- UoN-Ethics & Research Committee for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study
This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Yours sincerely,



PROF. M.L. CHINDIA
SECRETARY, KNH-UON ERC

c.c. The Principal, College of Health Sciences, UoN
The Senior Director CS, KNH
The Chairperson, KNH-UoN ERC
The Dean, School of Medicine,UoN
The Chair, Dept. of Surgery, UoN
Supervisors: Dr. John Ayugi(UoN), Dr. Sophie Gitonga(KNH), Dr. Catherine Nyongesa(KNH)

Appendix V: Originality Report

Pattern And Determinants Of Early Thyroid Hormone Profile Changes Following Radiotherapy For Head And Neck Cancers At The Kenyatta National Hospital.

ORIGINALITY REPORT

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3	Mark C. Weissler. "Thyroid-stimulating hormone levels after radiotherapy and combined therapy for head and neck cancer", Head & Neck, 09/1991 Publication	1%
4	Mehmet Koc. "Thyroid Dysfunction in Patients Treated With Radiotherapy for Neck", American Journal of Clinical Oncology, 04/2009 Publication	1%
5	Zhixiong Lin. "A Longitudinal Study on the	1%

10/09/2021

DR AYUGI

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PATTERN AND DETERMINANTS OF EARLY THYROID HORMONE PROFILE CHANGES FOLLOWING RADIOTHERAPY FOR HEAD AND NECK CANCERS AT THE KENYATTA NATIONAL HOSPITAL.

by Dr. Thomas Muthii Mureithi

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