POST RADIATION THERAPY HYPOTHYROIDISM IN PATIENTS WITH HEAD AND NECK CANCER AT PIETERSBURG HOSPITAL, LIMPOPO PROVINCE, SOUTH AFRICA

by

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DEDICATION

To my parents and brother, who showed me from an early age the importance of hard work.

To my family and friends for their patience and understanding in allowing me to work on this project.

Last, but certainly not least, I humbly dedicate this study to all cancer patients who unselfishly participate in research projects; without your valuable contribution, advancements in care would not be possible.

DECLARATION

I declare that POST RADIATION THERAPY HYPOTHYROIDISM IN PATIENTS WITH HEAD AND NECK CANCER AT PIETERSBURG HOSPITAL, LIMPOPO PROVINCE, SOUTH AFRICA is my own work and that all the sources that I have used or quoted have been indicated and acknowledged by means of complete references and that this work has not been submitted before for any other degree at any other institution.

Tijo Jospaul Davis Manavalan September 2021

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ABSTRACT

Background

Hypothyroidism in head and neck cancer patients after radiotherapy is known to occur, yet thyroid function tests are not routinely monitored in all patients post radiation therapy. Routine post radiation therapy thyroid function testing is currently not part of the follow-up protocol in these patients at Pietersburg Hospital.
The aim of this study is to evaluate post radiation therapy hypothyroidism among head and neck cancer patients treated with radiotherapy at Pietersburg Hospital

Methods

A prospective (cohort) observational study was carried out among head and neck cancer patients receiving radiotherapy at the radiation oncology department in Pietersburg Hospital. Sample size of n=37 was calculated using Statistica V13.0. Thyroid function tests were performed at the start of radiation therapy and repeated on the first day of follow up, 6 weeks after completing radiation therapy. During follow-up, participants were also interviewed for the presence of symptoms of hypothyroidism such as dry skin, dry hair, fatigue, cold intolerance, or weight gain. Data analysis was done with STATA version 16. Descriptive statistics were used to characterise variables, and summarised in tables, graphs and charts. Changes in thyroid function tests and other variables were analysed. A p-value of 0.05 was deemed statistically significant.

Results

Thirty-seven patients were enrolled in the study, 26 males and 11 females. The mean age of the patients was 53.1 ±12.3 standard deviation [SD]) with a range of 40.8 to 65.4 years. The most common diagnoses were cancer of the larynx and hypopharynx, forming 29.7% and oral cavity cancer, 29.7%. Only three patients (8%) had an early-stage cancer (Stages 1 and 2), 11 patients (29.7%) moderately advanced cancer (Stage 3) while the majority (62%; n =23) had locally advanced cancer (Stage 4).

Majority of the patients received 70Gy in 35 daily fractions, five fractions per week via 3-D conformal radiotherapy. Only 29 patients who had complete pre- and post-radiotherapy thyroid function tests were included in the final analysis. Of these, none had clinical hypothyroidism at 3 months. Two patients (6.8%) had sub-clinical hypothyroidism, with post radiation therapy TSH values greater than 3.5mIU/ml. The mean post radiation therapy TSH values increased by 8.3% and the mean fT4 values decreased by 2.05% compared to the pre-radiation therapy values. Both changes were not statistically significant (p=0.99 and p=0.82 respectively). There was no statistically significant correlation between changes in TSH and fT4 versus age (p=0.88 and p=0.92 respectively), sex (p=0.55 and p=0.15 respectively), cancer stage (p=0.21 and p=0.78 respectively), and cancer site (p=0.17 and p=0.74 respectively). The most common post radiotherapy symptom was fatigue (62%) followed by cold intolerance (54%), weight gain (43%) and dry skin or dry hair (43% each).

Conclusion

The results of the study suggest that sub-clinical hypothyroidism is detectable early post radiation therapy presenting as clinical symptoms.

Key words: thyroid function, TSH, fT4, thyroxine, radiotherapy, 3-D CRT

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DEFINITION OF KEY CONCEPTS

External beam radiation:

A method of delivering ionising radiation via a beam or several beams of high-energy x-rays to a tumour. Beams are generated externally and targeted toward the tumour (American College of Radiology, 2017). In this study external beam radiation refers to externally generated ionizing radiation used for treating cancers.

Gray (Gy):

The Gray is a unit of absorbed dose of radiation and has replaced the rad. 1 gray = 1 Joule/kilogramme = 100 rad (Baes, 2017). In this study Gray is used as the standard unit for the measurement of radiation dose.

Radical radiation:

Radiation therapy administered with an intention to cure (Rastogi, Revannasiddaiah, Gupta, Seam, Thakur and Gupta, 2012). This is in contrast to palliative radiation, which is administered with intent to palliate symptoms related to the tumour burden. In this study, radical radiation refers to curative radiation dose, whereas palliative radiation is a shorter course of radiation to alleviate symptoms in head and neck cancer such as pain, bleeding and physical deformity.

Fractionation:

Refers to the administration of the total dose of radiation in several parts at timed intervals to maximise the effect of radiation on the tumour and minimise side effects on the normal tissue (Al-Shammary, 2020). In this study radical radiation is administered at 2Gy per fraction per day, whereas palliative radiation is administered in 3Gy daily fractions.

Sparing:

This refers to the goal of minimising radiation dose to normal, healthy tissue while delivering sufficient dose to the tumour (Yazdani, Bouzarjomehri and Slessinger, 2019). In this study radiation shielding is done to spare normal tissues from unwanted radiation toxicity

Hypothyroidism:

Hypothyroidism refers to a condition where the thyroid gland is unable to produce adequate thyroid hormones to meet the metabolic requirements of the body (Dave, Klisiewicz, Bayat, Mohamed, Stevens, Mollentze and Kinvig, 2015). Hypothyroidism can be either primary or secondary. Primary hypothyroidism is caused by a thyroid disorder resulting in decreased production of thyroid hormones by the thyroid gland and a compensatory increase of TSH (Shahid, Ashraf and Sharma, 2018). Secondary hypothyroidism is caused by pituitary disorders and results in both decreased thyroid hormone and thyroid stimulating hormone (TSH) levels. Sub-clinical hypothyroidism refers to elevated TSH levels (higher than 3.5mIU/L) and normal free T4 (fT4) hormone levels without clinical symptoms, whereas clinical hypothyroidism is when TSH levels are elevated, but fT4 levels are low with or without clinical symptoms**.**

Cancer stage:

In this study, early stage head and neck cancers refers to stage I and II. Moderately advanced refers to stage III cancer, and locally advanced refers to stage IV cancer.

ECOG Performance scale (Eastern Cooperative Oncology Group, 1982)

Refers to the level of activity of a particular cancer patient as follows:

0 – Asymptomatic. Fully active, able to carry on all pre-disease activities without restriction

1 – Symptomatic but completely ambulatory. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).

2 – Symptomatic, <50% in bed during the day. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

3 – Symptomatic, >50% in bed, but not bedbound. Capable of only limited self-care, confined to bed or chair 50% or more of waking hours.

4 – Bedbound. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

5 – Death.

LIST OF ABBREVIATIONS

DAHANCA:	Danish Head and Neck Cancer Group
ENT:	Ear, Nose and Throat (also referred to as Otorhinolaryngology, Head and Neck Surgery)
fT4:	Free T4 Hormone
Gy:	Gray
HNC:	Head and neck cancer
HT:	Hypothyroidism
LT4:	Levothyroxine
mg:	Milligram
mIU:	Micro International Units
pmol:	Picomol
SEMDSA:	Society for Endocrinology, Metabolism and Diabetes in South Africa
TSH:	Thyroid Stimulating Hormone

CHAPTER ONE

1.1 INTRODUCTION AND BACKGROUND

Head and neck cancers (HNC) describe malignant tumours found in the various sub sites in the head and neck region. These include cancers of the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, salivary glands, sinonasal cavities, orbit, ear and neck. The latest publication from the Global Burden of Disease Cancer Collaboration, reports that certain cancers, such as laryngeal cancer have shown a global increase in incidence from an incident rate of 132 000 in 1990 rising to 211 000 in 2017 (Fitzmaurice, Abate, Abbasi, Abbastabar, Abd-Allah, Abdel-Rahman, Abdelalim, Abdoli, Abdollahpour, Abdulle and Abebe, 2019). Fitzmaurice *et al*., (2019) also note that incidence of cancer in several other sites has also increased. Notably, pharyngeal (excluding nasopharyngeal) site cancers showed the highest increase of all head and neck sites. The incidence of lip and oral cavity cancers increased from 186 000 in 1990 to 390 000 in 2017. This finding is supported by a surveillance, epidemiology and end results (SEER) population study which highlights that oropharyngeal cancer has demonstrated a “dramatic increase in incidence” (Mourad, Jetmore, Jategaonkar, Moubayed, Moshier and Urken, 2017). This trend of a dramatically increasing incidence in head and neck cancer cases pose a major public health crisis particularly in the developing world because these countries are projected to account for 70% of head and neck cancers by 2030 (Farmer, Frenk, Knaul, Shulman, Alleyne, Armstrong, Atun, Blayney, Chen, Feachem and Gospodarowicz, 2010).

Locally, the South African National Cancer registry places the incidence of head and neck cancers at just over 4.27% overall in the population (South African National Cancer Registry. Cancer in South Africa, 2014). However, these figures seem to underestimate the true numbers, as was noted in an article published in South Africa where the authors note that the true incidence might be higher than 10% (Hille and Johnson, 2017).

The main significance of these cancers is that they affect the entire face and upper aero-digestive tract causing cosmetic disfigurement and interference with respiration and overall nutrition. Standard management of HNC is based mainly on the anatomic location and stage of the tumour. Treatment response rates are good in early disease with 80 – 90% of patients attaining remission on optimum treatment. However, cure rates are poor in advanced stage disease (American Cancer Society, 2016).

Radiation therapy, alone or in combination with surgery and chemotherapy, features prominently as a principal treatment modality in both early stage and locally advanced head and neck tumours (Karapantzos, Zarogoulidis, Karanikas, Thomaidis, Charalampidis and Karapantzou, 2016). Most head and neck cancers are treated with radiation either as the primary definitive modality, or in the adjuvant setting post-surgery. According to the Danish Head and Neck Cancer Group report [DAHANCA], (2015), 70% of head and neck cancer patients from the European region received primary radiotherapy (Bjørndal, Krogdahl, Therkildsen, Charabi, Kristensen, Andersen, Schytte, Primdahl, Johansen, Pedersen and Andersen, 2015).

Owing to the rich lymphatic network of the head and neck region, the neck is often included in the radiation treatment portal, either as an elective treatment for suspected subclinical nodal metastatic disease at lower total radiation dose, or at higher dose to address gross nodal metastases. The anatomical location of the thyroid gland in the anterior neck places it at risk of receiving significant doses of radiation during the treatment of head and neck cancer by radiotherapy. This is accompanied by an increased risk of thyroid tissue destruction, which may predispose to developing hypothyroidism. In the ensuing hypothyroidism, decreased production of thyroid hormones by the thyroid gland due to destruction by radiation causes a compensatory increase of TSH (Shahid *et al.*, 2018).

Hypothyroidism after radiotherapy to the head and neck region is known to occur, and has been described as far back as in 1961 (Felix, Dupre and Drape, 1961). Several retrospective and a few prospective studies have examined the incidence of hypothyroidism after radiotherapy for head and neck cancer (Sinard, Tobin, Mazzaferri, Hodgson, Young, KunZ, Malhotra, Fritz and Schuller, 2000). Despite this,

hypothyroidism after radiation therapy is still an under recognised phenomenon (Rao, Sharma, Patel and Kothari, 2017).

In a study done in India, it was found that despite hypothyroidism having a significant impact on quality of life, assessment of thyroid function is not yet part of standard follow-up (Laway, Shafi, Majid, Lone, Afroz, Khan and Roohi, 2012). Nevertheless, Laway *et al.* (2012) find the incidence of hypothyroidism to be 23.5% at 2 years and recommended routine monitoring of thyroid function.

Srikantia *et al.* (2011) further state that post radiation therapy hypothyroidism remains under-estimated and under reported, due to the lack of routine thyroid function monitoring resulting in failure to detect and treat a reversible cause of morbidity in a large proportion of these patients.

A recent article that evaluated the progress of research in radiation-induced hypothyroidism in head and neck cancer patients notes that there is still no unified standard for the optimal thyroid gland dose threshold (Zhou, Chen, Tao, Chen, Yu and Chen, 2021). Other authors concur and posit that clear data were “scarce and inconsistent”, and that sub-clinical hypothyroidism is frequently missed because routine testing of thyroid hormones is not done during follow-up (Srikantia, Rishi, Janaki, Bilimagga, Ponni, Rajeev, Kaushik and Dharmalingam, 2011).

The aim of treating HNC focusses on improving efficacy while also reducing long-term morbidity. Therefore, special consideration should be given to the unique issues that affect HNC survivors as well as developing and adopting treatment guidelines that enhance quality survivorship.

Thyroid hormones assist in the regulation of some of the most basic and vital physiological processes in the body, including energy expenditure, substrate use, growth and development (Bhandare, Kennedy, Malyapa, Morris and Mendenhall, 2007). Hypothyroidism is associated with fatigue, weakness, weight gain, depression, poor memory and concentration, as well as the more serious conditions such as dyslipidaemias and cardiac arrhythmias. Hypothyroidism is generally an irreversible condition, which requires lifelong treatment with thyroxine administration. Fortunately,

replacement therapy normally reverses all signs of hypothyroidism, although neuromuscular or psychiatric symptoms could persist for several months (Garber, Cobin, Gharib, Hennessey, Klein, Mechanik, Pessah-Pollack, Singer and Woeber, 2012). The Society for Endocrinology, Metabolism and Diabetes in South Africa (SEMDSA) [2015] guidelines recommend treatment for patients with TSH above 4.0 mIU/L with L-Thyroxine (LT4) as the recommended replacement therapy.

This study evaluates hypothyroidism in HNC patients treated with radiotherapy at Pietersburg Hospital. Routine monitoring of thyroid function after radiotherapy in HNC patients does not currently form part of the follow-up protocol in the department. The outcome of this research could serve to guide the necessity and the frequency for monitoring thyroid functions in HNC patients after radiotherapy. This would allow for appropriate replacement therapy to be started early when indicated, in order to alleviate suffering.

1.2 RESEARCH PROBLEM

1.2.1 Source and background of the problem

In HNC patients, the symptoms of the cancer itself are very similar to those of hypothyroidism. Without a high index of suspicion, or routine monitoring of thyroid functions, cases of hypothyroidism could go undiagnosed, and untreated. Hypothyroidism is easily managed by replacement therapy, yet therapy cannot be commenced empirically without biochemical evidence of hypothyroidism (Dave *et al.*, 2015). Experts in the field highlight that the ramifications of subclinical hypothyroidism turning into overt hypothyroidism are especially grave in patients with HNC due to their high-risk profile (Aggarwal, Thakur, Rao and Shetty, 2020.).

There is a lack of knowledge on the burden of hypothyroidism after radiotherapy amongst HNC patients treated at Pietersburg Hospital. This study aims to evaluate hypothyroidism in HNC patients after radiotherapy with the purpose of quantifying it and describing any relationship that may exist between various clinical factors.

1.2.2 Statement of the research problem

The effects of locally administered radiation therapy on the thyroid are known to occur, with damage to thyroid tissue being evidenced by decreased functionality of the gland. The management of hypothyroidism is relatively easily achieved with replacement therapy where appropriate. The vague and non-specific nature of the symptoms of hypothyroidism, however, makes the diagnosis difficult in a cancer patient who may present with such symptoms from the disease itself. Thus, even if the history might be suggestive of hypothyroidism, without a high level of clinical suspicion and testing, it can still be under-diagnosed.

A study on the subject noted the importance of this. Chougule and Kochar (2011) conclude that hypothyroidism is known to have significant impact on quality of life of patients, but despite this, routine thyroid function tests are not yet included in the pre- or post- radiotherapy assessment protocols of patients with head and neck cancer.

In the radical treatment setting at Pietersburg Provincial Hospital's Radiation Oncology department, the neck is treated to a total radiation dose of 50Gy to address subclinical disease. Higher doses of up to 70Gy are used if there is gross disease in the neck. The thyroid gland may therefore receive between 50Gy to 70Gy. In the palliative care setting, doses administered vary between 8Gy and 39Gy, often given in a larger dose per fraction.

Currently, routine thyroid function assessment does not form part of the post-radiotherapy follow-up protocol.

1.3 PURPOSE OF THE STUDY

1.3.1 Research aim

The aim of the study is to investigate the prevalence of post radiotherapy hypothyroidism in patients with head and neck cancer treated at Pietersburg Hospital, Limpopo Province, South Africa.

1.3.2 Research objectives

The objectives are:

- To determine the prevalence of clinical hypothyroidism in head and neck cancer patients post radiation therapy at Pietersburg Hospital.
- To determine the prevalence of sub-clinical hypothyroidism in head and neck cancer patients post radiation therapy at Pietersburg Hospital.
- To investigate the relationship between the extent of hypothyroidism, radiation dose and the time of onset.

1.4 RESEARCH QUESTIONS

- What is the prevalence of clinical hypothyroidism in head and neck cancer patients post radiation therapy at Pietersburg hospital?
- What is the prevalence of sub-clinical hypothyroidism in head and neck cancer patients post radiation therapy at Pietersburg hospital?
- What is the relationship between the extent of hypothyroidism, radiation dose, and the time of onset?

1.5 RESEARCH METHODOLOGY

1.5.1 Research design

A prospective (cohort) observational study of the thyroid functions in head and neck cancer patients receiving radiotherapy was carried out.

1.5.2 Sampling

All consecutive head and neck cancer patients referred to the combined head and neck clinic at Pietersburg Hospital for radiotherapy were eligible to participate. The inclusion and exclusion criteria are elaborated on in chapter 3. Sample size of n=37 was calculated using a paired t-test in Statistica programme V13.0.

1.5.3 Data collection

Blood samples for thyroid function tests were collected at the start of radiation therapy. The tests were repeated on the first day of follow-up 6 weeks after radiation therapy. Patients were also interviewed for the presence of any symptoms of hypothyroidism such as dry skin, dry hair, fatigue, cold intolerance, or weight gain at this visit. The researcher collected data using the data collection sheet adapted for this study (Annexure A).

1.5.4 Data analysis

Descriptive statistics (means, proportions, frequency) were used to characterise the variables such as age, radiation dose, and TSH and fT4 levels. The details are summarised in frequency tables, graphs, and charts in chapter 5. A Kruskal-Wallis test and a Mann-Whitney test were used to analyse the association between any change in thyroid function tests and the variables. Wilcoxon signed rank test was used to study the effect of radiotherapy on thyroid function. A *p*-value of <0.05 was considered statistically significant.

1.5.5 Reliability, Validity and Objectivity

Reliability, specifically that concerning the consistency of laboratory testing of the specimens, was ensured by processing and analysis of all blood samples in the laboratory using a Beckman Access® immuno-analyser.

Regarding validity, internal and external validity were both taken into consideration in the study. Internal validity was maintained by ensuring that all patients who satisfied the inclusion criteria were given a chance to enrol. External validity is ensured by using statistical methods to evaluate the relationship between the variables that may influence thyroid functions among the patients. It is therefore possible to generalise the result from this cohort of patient to any other patient with head and neck cancer receiving radiotherapy.

Objectivity pertaining to the interview of the patient was maintained by utilising the same data collection sheet for all participants. This minimised variability in the conduct of the interview.

1.5.6 Bias

During recruitment, all patients who presented were eligible to enrol. Secondly, the measurement of outcomes used numerical data variables, followed by statistical analysis of the data. Lastly, available data for all patients recruited in the study were captured to ensure that all outcomes are consistently reported.

1.6 ETHICAL CONSIDERATIONS

The principles of good medical ethical practice were observed at all stages in the study. In particular, the tenets of not causing harm (non-maleficence), autonomy, anonymity, confidentiality, and beneficence were adhered to. The particulars of each of these are discussed in detail in chapter 3. Ethical clearance to conduct the study was obtained from the Turfloop Research and Ethics Committee (TREC), with the project number: TREC/415/2017: PG (Annexure D) and TREC/415/2017: PG-Renewed (Annexure E). Ethical clearance was also granted by the Pietersburg/Mankweng Research Ethics Committee with reference: PMREC 21 JULY UL2021/C (Annexure G). Permission to conduct the study was obtained from the Limpopo Provincial Department of Health with reference number: LP_2021-08-021 (Annexure F).

1.7 SIGNIFICANCE OF PROPOSED RESEARCH

The study can contribute towards protocol adjustments in the radiation oncology department at Pietersburg Hospital to incorporate routine biochemical monitoring of thyroid function in the follow-up of head and neck cancer patients after radiation. Patients found with hypothyroidism would be appropriately referred to be initiated on replacement therapy.

1.8 CONCLUSION

The main findings regarding thyroid function were that none of the patients developed clinical hypothyroidism. Only two patients (6.8%) developed sub-clinical hypothyroidism at 3 months after radiotherapy. The findings were not statistically significant. The correlation between changes in TSH and fT4 to radiation dose were not statistically significant with p-value of 0.99 and 0.82 respectively.

1.9 OUTLINE OF THE DISSERTATION

This dissertation comprises of five chapters. Chapter 1 lays out the background and introduces the ideas that are fundamental to understanding the current situation in post radiotherapy hypothyroidism in head and neck cancer patients. The purpose of the present study, together with its aims and objectives are detailed. The rest of the chapter briefly summarises the research methodology, ethical considerations, and findings. Chapter 2 examines various studies on the topic and their findings, together with their strengths and shortcomings. Chapter 3 details the research methodology. The ethical considerations and ethical principles pertinent to medical ethics are laid out. Data analysis, together with measures taken to maximise reliability and validity while minimising bias are also described. Chapter 4 presents the results of the study which are aligned to its objectives. In chapter 5, the findings of the study are discussed. The chapter explores both limitations and contributions of the study, and makes recommendations for future studies on the topic.

CHAPTER TWO

2. LITERATURE REVIEW

2.1 INTRODUCTION

This chapter examines the literature available in the field. The chapter starts by highlighting the impact of head and neck cancers and presents data on the mortality and morbidity it poses. Although most published research is from the developed world, some studies from developing countries in Asia as well as those done in South Africa are included in an attempt to reflect a more contextually relevant picture. The remainder of the chapter is structured in line with the research project's objectives, to provide context to the reader. The section presents overviews of prior research including the most recent publications in 2021, looking at the findings and shortcomings as well as the recommendations made for further studies. Of note is that although some studies discussed are older, they are however landmark studies in the field which resulted in guideline documents emanating from them.

2.2 EPIDEMIOLOGY OF HEAD AND NECK CANCERS

The term head and neck cancer encompass a heterogeneous group of cancers in the entire region of the head and neck, although squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx and larynx are the most common (Rønjom, 2016). Globally, head and neck carcinomas are ranked as the sixth most common cancer overall in the latest statistics published in 2017 (American Cancer Society, 2017).

Head and neck cancers account for about 4% of all cancers in the United States. The American Cancer Society projects that, 66 630 people (48 740 men and 17 890 women) will develop head and neck cancer in America in 2021. It further projects that 14 620 deaths (10 640 men and 3 980 women) from head and neck cancer will occur in 2021 in America (American Cancer Society, 2021). Globally, the Global Cancer Observatory (GLOBOCAN) estimates that 705 781 cases and 358 144 deaths occurred worldwide due to lip, oral cavity, oropharyngeal, and hypopharyngeal cancers in 2018. Males are significantly more likely to develop HNC than females with

an incidence ratio ranging from 2:1 to 4:1 (Bray, Ferlay, Soerjomataram, Siegel, Torre and Jemal, 2018).

The SEER population study also highlights that cancers of the oropharynx have demonstrated a “dramatic increase in incidence” (Mourad *et al.*, 2017). This trend is also noted in a study published on the epidemiological trends of head and neck cancers in Alberta, shown in Figure 2.1 (Song, Vallance, Biron and Jeffery, 2020).

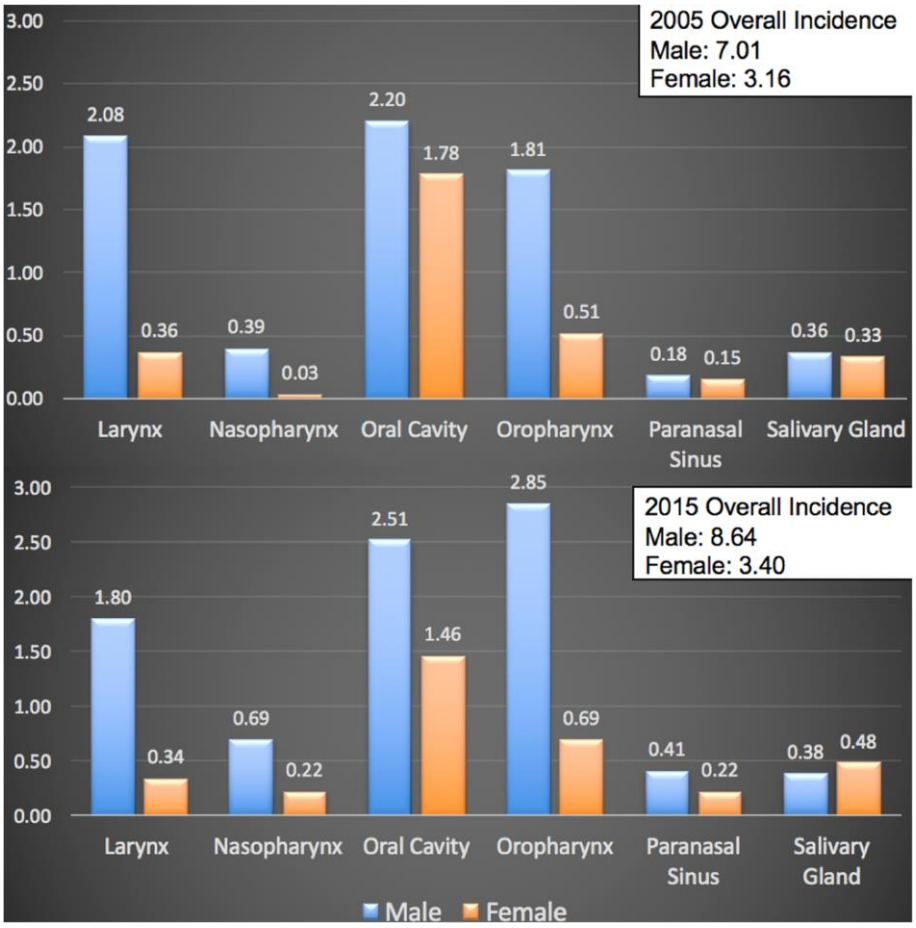


Fig 2.1 Incidence changes 2005 vs 2015 rate per 100 000 of head and neck subsites (Song *et al*., 2020).

Looking at the developing world, the trend of a dramatically increasing incidence in head and neck cancers’ cases posing a major public health crisis was noted as early as 2010 in a study published in the Lancet which projected that developing countries would account for 70% of head and neck cancers by 2030 (Farmer *et al.,* 2010). This trend is graphically depicted in figure 2.2, below (Fagan, Stannard and Dalvie, 2014),

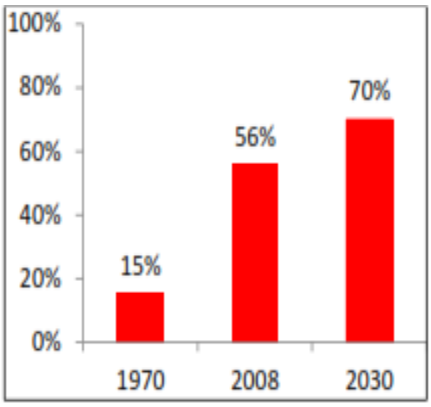


Fig 2.2 Rising incidence of cancers in developing countries (Fagan, *et al*., 2014)

2.2.1 Mortality and Morbidity of head and neck cancers

Approximately 30%–40% of head and neck cancer patients in the United States present with early-stage disease, resulting in a 5-year survival of 70%–90% with treatment (Hsu, Chan, Yin, Lee, Chern and Liao, 2019). This suggests that most head and neck cancers are diagnosed at advanced stages, when medical treatment is less effective and surgical treatment would be mutilating to organs required for speech and swallowing. When discussing the mortality and morbidity of head and neck cancers, it is imperative to be aware of the differences in outcomes in different countries.

For individuals in countries with limited access to tertiary level health care, the 5-year survival rates are much lower and range between 30%–40% (Pruegsanusak, Peeravut, Leelamanit, Sinkijcharoenchai, Jongsatitpaiboon, Phungrassami, Chuchart and Thongsuksai, 2012; Sinha, Anderson, McDonald and Greenwald, 2003; Nandakumar, 2016). The global differences in outcomes become clearer when one considers that approximately two-thirds of all head and neck cancer patients survive in the United States (Hsu *et al.*, 2019). Furthermore, in the United States except for the tongue and oropharyngeal/tonsillar cancers, the 5-year survival has increased in the two decades prior to 2012 (Solca, Dahl, Zoephel, Bader, Sanderson, Klein, Kraemer, Himmelsbach, Haaksma and Adolf, 2012). Supporting this data was a large analysis of the SEER database, which showed that the overall 5-year relative survival rate across head and neck cancers increased from 54.7% in 1992–1996 to 65.9% in 2002–2006 (Pulte and Brenner, 2010).

In the developing countries, oral cancer was found to be the third most common with a higher mortality in black men as compared to their white or Hispanic counterparts (Johnson, 2001; Coelho, 2012; Warnakulasuriya, 2009). An article comparing the burden of head and neck cancers in Australia with India reveals large differences in mortality and morbidity across the two countries within the different socio-economic levels (Singh, Eisenberg and Hoffman, 2018). This study also notes a global incidence of head and neck cancer of 900 000 cases in 2017, of which 470 000 were diagnosed in India alone, head and neck cancers being the second most common cancer in this population (NICPR, 2017).

In Africa, oral cavity cancers constitute a significant proportion of the global cancer burden. However, the complexity and variability in anatomy-based head and neck cancer nomenclature has led to an underestimation of its incidence as well as its impact (Adeola, Afrogheh and Hille, 2018). This is illustrated in an earlier study which describes the incidence of oral cancer in Kenya as very low (Kaimenyi, 2004). However, Adeola *et al*. (2018) find that the initial lower incidences may have been due to under-reporting. The apparent under-reporting of these cases in many parts of Africa is due to a multitude of factors, including lack of cancer registries, lack of cancer control programmes, poor health infrastructure, poor access to healthcare, financial constraints, lower educational levels and existing religious and cultural beliefs (Adeola *et al.,* 2018).

In South Africa, an increasing trend in the incidence of head and neck cancers have been noted over the years from 1992 to 2001, especially amongst the coloured population compared to other ethnicities (Ayo-Yusuf, Lalloo and Johnson, 2013). This study also found that blacks had the lowest incidences, but other authors feel that this is questionable and thought it was almost certainly due to poor access to healthcare, especially in the rural areas (Adeola *et al.,* 2018).These authors lament the lack of locally derived data on head and neck cancers and state that the true burden of disease is actually unknown in this region due to the poor documentation of cases, poorly defined nomenclature and a lack of functioning cancer registries across the continent (Adeola *et al.,* 2018).

2.3 Treatment Modalities for head and neck cancers

Radiotherapy, chemotherapy, and surgery all play a role in the treatment of head and neck cancers, mostly used in combination. However, high dose radiotherapy is often used for cure in some instances besides surgery in the treatment of these cancers (Srikantia *et al*., 2011).

2.3.1 Radiation Therapy

Regarding radiotherapy for head and neck cancers, primary radiotherapy is mostly delivered via a linear accelerator with 6-megavolt photons. The anatomic site of the tumour and required depth of penetration are the main criteria in choosing the modality, the dose, and the energy of external radiotherapy utilised (Leeman, Tsai and Lee, 2020).

Radiation is typically directed to the areas of gross tumour as well as regions suspected to be at risk of microscopic tumour involvement. These “elective” treatment volumes are defined based on known patterns of lymphatic spread of head and neck cancers and are therefore at risk of harbouring disease (Leeman *et al.*, 2020).

2.4 Hypothyroidism post radiation therapy

Hypothyroidism is known to be a potential consequence of external beam radiotherapy to the head and neck region, with the first case being described as far back as 1961 (Felix *et al.*, 1961). Several retrospective and a few small prospective studies have examined the incidence of hypothyroidism after multimodality treatment for head and neck cancer (Sinard *et al.,* 2000). In spite of this finding, hypothyroidism after radiation therapy is still an under-recognised phenomenon (Rao *et al*., 2017).

In a 2021article which reported the research progress made in radiation-induced hypothyroidism in head and neck cancer patients, the authors note the lack of a unified standard for the optimal thyroid threshold. The authors recommend that prospective studies with large samples and longer-term follow-up should be carried out in this field

to contribute to better understanding of this topic (Zhou, Chen, Tao, Chen, Yu and Chen, 2021).

A study done in India also finds that despite hypothyroidism having significant impact on quality of life, assessment of thyroid function is not yet part of routine follow-up in head and neck patients post radiotherapy. The study finds the incidence of hypothyroidism to be 23.5% at 2 years and concludes that hypothyroidism occurs with "considerable and poorly acknowledged frequency" and recommends routine monitoring of the thyroid function (Laway *et al.*, 2012).

Another study on the subject finds that clear data was "scarce and inconsistent". The authors further say that sub-clinical hypothyroidism is frequently missed because routine testing of thyroid hormones is not done during follow-up (Srikantia *et al.*, 2011). Srikantia *et al.* (2011) go on to state that hypothyroidism as a result of radiation therapy, has remained under-estimated and under reported, due to the lack of routine thyroid function monitoring. The authors follow this by saying that lack of monitoring results in failure to detect and treat a reversible hypothyroidism-caused morbidity in a large proportion of patients.

In a different study, the authors note that when radiotherapy is used to treat head and neck cancers the exposure of non-target tissues including the thyroid, cannot be avoided and hypothyroidism can develop months to years after the exposure (Rønjom, Brink, Bentzen, Hegedüs, Overgaard, Petersen, Primdahl and Johansen 2015). These researchers conducted a prospective study evaluating 203 patients with head and neck cancer, from which they estimated the 5-year incidence of post radiotherapy hypothyroidism to be 26%. There was quite a range in treatment doses administered, with the median thyroid dose being 40Gy (the minimum was 1.2Gy and the maximum 68Gy). The study concludes that main risk factors for the development of hypothyroidism was a small thyroid volume as well as a high mean radiation dose to the gland (Rønjom, Brink, Lorenzen, Hegedüs and Johansen 2015). Another prospective observational study of 68 patients evaluating thyroid function in patients with nasopharyngeal cancer from baseline to 48 months post radiotherapy finds that mean TSH levels increase shortly after radiotherapy, peaks at 18–24 months, and

then decrease, albeit remaining elevated above an upper level of normal of 4.0 miU/L (Lin, Yang, He, Wang, Gao, Tam and Wu, 2018).

When it comes to the actual incidence of post radiotherapy hypothyroidism, the literature shows a very wide range. A study published in 2014 finds the incidence to be 6% overall (Khurram, Fauzia, Robert, Lara, Arezo, Saif, Wajiha, Carlos, Farah and Dat, 2014). In this retrospective study Khurram *et al.* (2014) analysed the records of 1116 patients with head and neck cancers who received radiation therapy over a period of 13 years. Their findings reveal the incidence of hypothyroidism to be higher in the African American patients (7.6%) as compared to a similar group of white patients (6%). They also find that gender was a stronger predicting factor for developing hypothyroidism as females were 1.90 times more likely to develop hypothyroidism than males were (95% CI 1.17-3.09).

However, another study reports a higher incidence of hypothyroidism after radiotherapy in head and neck cancer patients. This study found an incidence of 47.7% at a median of 1.08 years after radiation (Diaz, Jaboin, Morales-Paliza, Koehler, Phillips, Stintson, Gilbert, Chung, Murphy, Yarbrough, Murphy, Shyr and Cmelak, 2010). Again, this was a retrospective study and here Diaz *et al.* (2010) analysed serial TSH levels during follow-up visits of 128 patients who received radiation therapy for up to 3 years, in which 61 patients developed hypothyroidism by the end of the study period. In this study the thyroid gland received doses as high as 70Gy.

One of the larger recent prospective studies finds that the incidence of hypothyroidism rose over time after receiving radiation (El-Shebiney, El-mashad, El-Mashad, El-Ebiary and Kotkat, 2018). This was a single arm study of 78 patients conducted over 3 years. It involved an evaluation of baseline thyroid function followed by repeat assessments at all scheduled follow-ups. In this study it was found that the median cumulative incidence of hypothyroidism was 24.6%, 36.5% and 42.3% at one, two and three years respectively. In absolute numbers, out of the 78 patients, 33 had developed hypothyroidism by 37 months. Importantly, 27 out of these 33 had overt/clinical hypothyroidism, and the remaining 6 had subclinical hypothyroidism.

An earlier prospective study involving 104 patients reveals post treatment hypothyroidism of 23% (Turner, Tiver, and Boyages, 1995). In this study pre-treatment baseline thyroid hormone levels were measured. Out of the 20 patients who developed hypothyroidism, 12 (60%) had clinical hypothyroidism and 8 (40%) had subclinical hypothyroidism.

Another retrospective study investigated the incidence of hypothyroidism in patients with oral tongue carcinoma (Kumari, Gondi, Nemade, Rao, Gudipudi, and Rao, 2017) The authors find the incidence of hypothyroidism to be 21.5% at a median follow-up of 32 months, in addition to finding that hypothryoidism was picked up as early as at 3 months after radiotherapy.

A prospective observational study published in 2014, evaluated 114 patients over a period of 2 years from October 2008 to October 2010. In this study, thyroid function tests were done before radiotherapy and repeated at 1 month, 6 months, 1 year and 2 years after radiation therapy. The findings reveal the prevalence of hypothyroidism to be 46% at median time of 8 months after radiation therapy (Kim, Yu and Wu, 2014). Patients in the study received doses ranging from 44Gy – 67.5Gy in total. This is one of the largest prospective studies on this topic with a longer period of follow-up.

It is thus clear, based on the literature, that the studies reflect a wide range in incidence of post radiation as well as a wide variation in the time to onset of hypothyroidism. It is also clear, that there are not many studies that were done prospectively, and there are none to the researcher's knowledge that have been done in Sub-Saharan Africa on this topic.

2.4.1 Relationship between total radiation dose and hypothyroidism

The pathogenesis of thyroid tissue damage after radiation includes an autoimmune reactions and vascular and parenchymal damage (Jereczek-Fossa, Alterio, Jassem, Gibelli, Tradati and Orecchia, 2004). Studies conducted on dogs find that exposure to external radiation of as little as 2.4-3.8 Gy leads to thyroid hypofunction. Several structural changes, including, but not limited to stromal and vascular sclerosis,

perivascular oedema, effusion of colloid into the interstitial tissue, desquamation of epithelium and disintegration of individual follicles were also seen (Grigoryev, 1989). Direct damage to the thyroid gland from a fractionated radiation dose >18Gy, most often presents with hypothyroidism, with low T4 and elevated TSH (Cohen, 2005).

Based on the report from the literature, the incident of hypothyroidism occur at different radiation doses. The diversity of thyroid gland radiation dose limits motivated the National Cancer Institute to establish a task team to review literature on this subject and come up with a common recommendation. The task team found that the 5-year risk of developing thyroid dysfunction is 5% after a 45Gy dose, and 50% with an 80Gy dose (Emami, Lyman, Brown, Coia, Goitein, Munzenrider, Shank, Solin and Wesson, 1991). Albeit somewhat older, this document still provides the dose limits used in daily practice clinical practice of radiotherapy (Emami *et al*., 1991).

A later study finds that both acute and late effects on the thyroid gland are evident after radiation doses ranging from 30Gy up to 70Gy. This study looked at the relationship between the radiation dose the thyroid and incidence of hypothyroidism as evaluated by TSH and fT4 levels. The study finds the incidence of hypothyroidism to be significantly lower in patients who received a mean dose to the thyroid gland of less than 30Gy. The potential shortcoming of this study is that it is retrospective and included only 75 patients who had no baseline thyroid function values (Fujiwara, Kamikonya, Tanooka, Miura, Doi, Takada, Terada, Uwa, Sagawa and Hirota, 2012).

Other studies found evidence of thyroid gland damage at much lower doses. One study found that thyroid gland damage can be demonstrated histologically at radiation doses as low as 2.25Gy (Hancock, McDougall and Constine, 1995). A study done in 2019 finds that TSH levels increased from 0.88 ± 0.55 (pre-radiotherapy) to 1.7 ± 0.66 (post-radiotherapy) ($p < 0.05$). The researchers studied 30 head and neck cancer patients before and after completion of radiation therapy which involved collection of baseline thyroid function tests and repeating the tests upon completion of the radiation therapy. The change in TSH values pre- and post-radiotherapy was statistically significant (Yazdani et al., 2019).

Another recent prospective study finds that the incidence of hypothyroidism increases over time after receiving radiation (El-Shebiney *et al.*, 2018). This study evaluated the radiotherapeutic factors that affect the incidence of hypothyroidism after radiation therapy in 78 head and neck cancer over 3 years. It involved an evaluation of baseline thyroid function followed by repeat assessments at 1, 6, and 12 months and then annually. It reports that the most significant predictor of the developing hypothyroidism after radiation is the volume of the thyroid gland receiving a dose equal to or greater than 30Gy.

With technological advances in delivery of radiation therapy where higher radiation doses can be delivered to the tumour volumes with increased sparing of the surrounding normal tissues, the dose threshold for hypothyroidism in head and neck cancer patients need to be studied further (Zhou *et al.,* 2021). However, even the most recent guidelines for the quantitative analysis of normal tissue effects in the clinic (QUANTEC) which specifies safe dose limits for many tissues failes to mention a dose limit for the thyroid gland (Bentzen, Constine, Deasy, Eisbruch, Jackson, Marks, Ten Haken and Yorke, 2010).

2.4.2 Onset of hypothyroidism post radiotherapy

Hypothyroidism can be detected shortly after the onset of radiation therapy or after several fractions of the dose. Several studies looking at this relationship, report considerable variations of their findings. In an Australian study the rise in thyroid stimulating hormone (TSH) levels is found to occur as early as 4 weeks post radiation therapy (Turner *et al.*, 1995). This trend is supported by conclusion from a review article published many years later from the USA which states that the onset of hypothyroidism can occur as early as 4 weeks and as late as 5 or 10 years. They note that the incidence of hypothyroidism after radiation therapy was 26% at 2 years and continued to rise to 62% at 6 years (Miller and Agrawal, 2009). However, another study finds that the average time to detection of hypothyroidism is 8.2 months, with the range from 1 to 21 months. This study thus recommends thyroid function assessments to be measured at 3 months post radiation (Sinard *et al.*, 2000). A study from India which evaluated thyroid function with tests done at the start of radiotherapy and repeated on

completion of radiotherapy treatment at 3 months, at 6 months, and thereafter every 6 months, finds that mean TSH values showed a rising trend from baseline values until 180 days ($P<0.05$) (Banipal, John, Mahajan and Uppal, 2011).

Most of these studies recommend that thyroid function tests generally be done in the first 1-2 years after the end of treatment. This contrasts other (mostly older) studies, that find that the median interval to development of hypothyroidism was 1.4 years to 1.8 years and thus suggest later, rather than earlier, monitoring of thyroid function (Tell, Lundell, Nilsson, Sjödin, Lewin and Lewensohn, 2004; Mercado, Adelstein, Saxton, Secic, Larto and Lavertu, 2001).

One of the only published studies on this subject from Africa was done in Egypt in 2018. Seventy-eight patients were monitored for a maximum of 3 years, of which 33 participants in the group (42.3%) had developed hypothyroidism at a median of 31 months (range:18-37 months). The incidence at 1 and 2 years was 24.6%, 36.5% respectively (El-Shebiney *et al.*, 2018).

A prospective observational study in 2019 involving 30 head and neck cancer patients evaluated thyroid function at the start and repeated at the end of the radiation therapy. Despite the shorter duration of follow-up, the authors were still able to demonstrate a statistically significant rise in post-radiation TSH values 1 month radiotherapy (Yazdani *et al.*, 2019). The patients received between 44Gy and 60Gy in fractions of 2Gy each.

2.5 Conclusion

The accessed literature seems to suggest that, despite several studies which looked at the time of onset of hypothyroidism after radiation therapy, there is a wide variability in their recommendations. It is still not clear as to when to start monitoring thyroid functions. Furthermore, most of the studies are retrospective in nature, with baseline thyroid function assessments not being done before radiation.

CHAPTER THREE

3. RESEARCH METHODOLOGY

3.1 INTRODUCTION

This chapter describes the methods and the design selected for this research project. The factors that influenced its selection are explained. There is also a discussion on the steps taken to ensure validity and reliability of the findings, in addition to an outline of the statistical methods used to analyse the data.

3.2 RESEARCH DESIGN

A prospective (cohort) observational study of the thyroid functions in head and neck cancer patients receiving radiotherapy was carried out. A prospective design (also called cohort design) is a study design in which a researcher starts with a presumed cause and then go forward in time to the presumed effect (Polit and Beck, 2017:204).

An observational study is one in which the investigator does not intervene but assesses the relationship between an exposure and a variable (Merrill, 2019:154). The design was chosen for this study because it is the strongest design for studying prognosis and aetiology when randomisation is not possible (Polit and Beck, 2017: 204). In this study patients with head and neck cancers treated with radiotherapy were observed for the effect of radiotherapy on thyroid gland functions, because the thyroid gland is inadvertently included in the radiotherapy field.

3.2.1 Sampling

3.2.1.1 Study setting

The study was conducted at the radiation oncology department in Pietersburg Hospital (a combined medical and radiation oncology facility). Pietersburg Hospital is an

academic hospital affiliated to the Faculty of Health Sciences in the University of Limpopo. It is located in the city of Polokwane, the provincial capital of Limpopo. Pietersburg Hospital serves as the referral centre for all regional hospitals from the five districts in Limpopo province, namely: Capricorn, Sekhukhune, Mopani, Vhembe and Waterberg.

The radiation oncology department is the only radiation therapy facility in the public sector in Limpopo province. In addition to serving the province, it also serves patients from neighbouring countries (Botswana and Zimbabwe) due to its geographical location and sharing of common state boundaries with these countries.

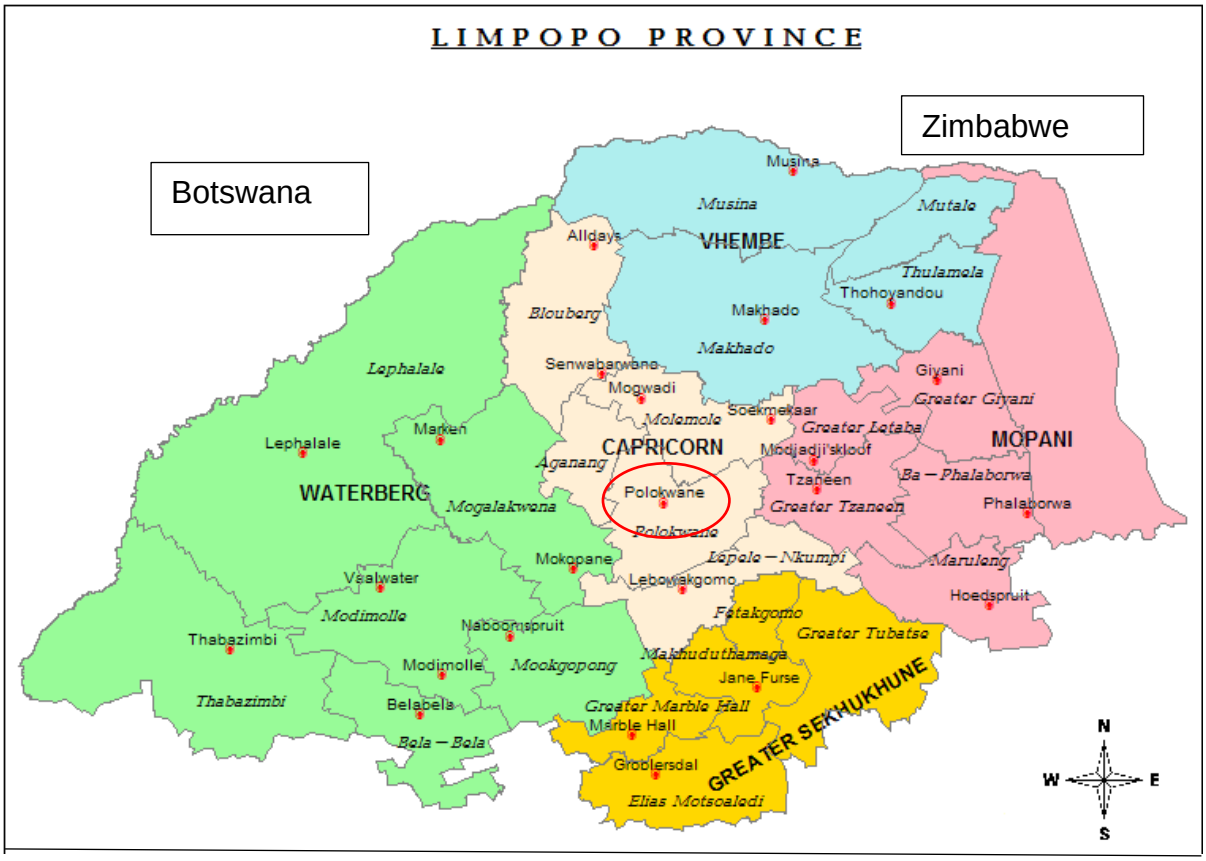


Figure 3.1 Map of Limpopo (Mahlangu, N. and Legothoane, A., 2013)

Patients with head and neck cancer are referred from the department of otorhinolaryngology to the combined head and neck oncology clinic, a multi-disciplinary clinic attended by specialist teams from otorhinolaryngology, Head and Neck Surgery (ENT), Maxillo-Facial-Oral Surgery (MFOS) and clinical oncology departments. The multidisciplinary team assesses the patients and reach a consensus

on management plan. Once decision is made for the patient to be offered radiation therapy, they are then booked and the necessary pre-treatment preparations completed.

3.2.1.2 Population

A study population is the entire set of individuals or objects having some common characteristics from which some information is required to be ascertained (Banerjee and Chaudhaury, 2010). In this study, the population comprised all head and neck cancer patients referred to the combined head and neck clinic at Pietersburg Hospital during the period of the study.

3.2.1.3 Study sample

A sample is a sub-set of the defined population comprising those selected to participate in a study (Polit and Beck, 2017:743). In this study the sample consisted of consecutive patients seen at the combined head and neck clinic that met the specified criteria.

The inclusion criteria were:

- Age above 18 years old.
- Life expectancy of greater than 6 months
- Eastern Cooperative Oncology Group (ECOG) score of 2 or less or Karnofsky Performance Status >60%
- Anticipated to be treated with external beam radiation therapy portals that covered the neck, and therefore the thyroid gland.
- Consented to participate in the study

Exclusion Criteria:

- Patients with primary malignancies of the thyroid gland or a prior history of any thyroid disorders. These diagnoses themselves were likely to affect the thyroid functions prior to radiotherapy.
- Patients with primary malignancies in the nasopharynx.

- ECOG performance scale of 3 or 4
- Estimated life expectancy less than 6 months
- Refusal to take part in the study

Patients with nasopharyngeal malignancies were excluded because when these patients receive radiation treatment, the target field encroaches on the hypothalamus, affecting the integrity of this organ, and thus places them at risk of developing secondary hypothyroidism due to hypothalamic hypofunction.

3.2.1.4 Sampling method

The potential participants who met the inclusion criteria, were identified at the combined head and neck oncology clinic but were enrolled into the study on their first day of radiotherapy. This was done to avoid losing the participants before they commence their planned radiation treatment. Sample size of n=37 was calculated by Statistica programme V13.0, on a reduction of 15% after 30 days of radiation therapy in fT4=12.8, with a power of 80% and a significance level of 5% (reduction of -23.5% of fT4 after 30 month of radiation therapy) (Lin *et al.*, 2018).

3.2.2 Data Collection

3.2.2.1 Data collection approach and method

The participants underwent radiation therapy as part of the expected treatment for their specific cancer diagnosis.

Blood samples for thyroid function tests were collected at the start of radiation therapy. The tests were repeated on the first day of follow up, 6 weeks after radiation therapy, and the patient interviewed for the presence of any symptoms of hypothyroidism such as dry skin, dry hair, fatigue, cold intolerance, or weight gain.

- *Radiation therapy*

All patients were seen by the dietician and had a dental assessment in preparation for radiation therapy. After a discussion on side effects and precautions during radiation, informed consent was obtained. A computed tomography (CT) scan of the head and neck region, with intravenous contrast media was then performed on the Philips Brilliance CT Scanner in the treatment position. This process is known as CT simulation and is necessary for treatment planning. All patients were scanned in a supine position, on the simulator flat top couch. The head, neck and shoulders were immobilised in a 5-point thermoplastic mask. Shoulder traction was used during CT simulation. After CT scan, the images were transferred to the planning system.
Target volumes (tumour and neck lymphatics) and organs at risk were defined and delineated according to consensus guidelines and department protocols. Treatment was planned on the Eclipse (V8.0 and V15.60.6) radiotherapy treatment planning system. Dose volume histograms were created for all treatment plans. The radiation oncologist then evaluated the radiation treatment plan and approved it as per the normal departmental clinical protocols. Dosimetry and plan quality assurance was then completed by the medical physicists.

Patients received the prescribed radiation therapy appropriate for their diagnoses and the stage of their cancer. Treatment was performed with photons using 6-MV Varian linear accelerator (Varian Medical Systems, Palo Alto, CA, USA). The medical physicists calibrate the linear accelerator daily as part of the equipment quality assurance checks to validate the positioning and radiation dose outputs. Individual patient treatment quality assurance checks were performed at several steps in the process. The simulation and planning parameters were checked and compared with that during treatment set-up by obtaining portal images. Portal verification images and digitally reconstructed images were obtained and compared to verify accuracy of the positioning. Portal imaging is done for the first three treatments, and thereafter weekly.

Patients treated with curative intent received between 50-70Gy total radiation dose, delivered in fractions of 2Gy per day, 5 days per week, over 5 to 7 weeks. One exception was a case of adjuvant radiation for a Hodgkin's lymphoma who received the recommended dose of 36Gy in 2Gy fractions to the neck. The intent here was still

curative. The patients who received palliative intent radiation received 39Gy total dose, given at 3Gy per fraction per day, 5 days a week over 3 weeks.

During radiotherapy all patients were reviewed by the radiation therapy clinical team at least once per week. During this review a clinical examination was conducted, and blood tests and results were reviewed. Side effects to treatment were monitored and appropriate treatment prescribed. If the patient was due for concurrent chemotherapy, these were prescribed.

3.2.2.2 Development of the data collection instrument

The data collection instrument was adapted from one previously used for the same type of study (Srikantia *et al.,* 2011).
Data collected included:

- Thyroid function tests to determine the prevalence of sub-clinical and clinical hypothyroidism.
- Radiation dose administered, to evaluate for any correlation between radiation dose and onset of hypothyroidism if present
- Disease and basic demographic data of the patient
- Clinical features of hypothyroidism, if present.

3.2.2.3 Data collection instrument

Data collection was done by the researcher, using the data collection sheet adapted for this study (Annexure A). The patients' demographic data, including age, gender, and relevant past medical history were entered in section (A). The clinical data including tumour site, the stage of the cancer, histological type, the patient's performance status and radiotherapy details were recorded in section (B). The patients reported clinical symptoms of hypothyroidism were recorded in section (C). The blood test results for thyroid stimulating hormone (TSH) and free thyroid hormone (fT4) levels were recorded in section (D) of the data sheet.

3.2.2.4 Data collection process

- *Thyroid function tests*

On the first day of enrolment, after providing informed consent, approximately 1-2ml of venous blood was drawn from a peripheral vein in a BD Vacutainer SST II Clot activator tube with gel (Gold/Yellow topped tube). Blood tests were processed at the National Health Laboratory Services (NHLS) Laboratory at Pietersburg Hospital on the collected blood sample. Bloods for both thyroid stimulating hormone (TSH) and free thyroxine (fT4) levels were processed and measured by radioimmunoassay using standard commercial laboratory methods, with the Beckman Access® test being utilised by the NHLS. Patients were asked about the use of any medications that may influence thyroid function levels.

On the last day of radiation therapy, the patients were given an appointment for their first review visit in 6 weeks post radiotherapy (approximately 3 months after starting radiation therapy) and discharged home. Thyroid function tests were repeated at this follow-up review. In addition to blood collection, the patient was evaluated for the presence of any signs and symptoms of hypothyroidism.

3.2.3 Ethical considerations

Medical research involving humans is subject to ethical standards that promote and ensure respect for all human subjects and protect their health. The Helsinki declaration on ethical principles for medical research involving human subjects (World Medical Association, 2013) were adhered to throughout the research project. Locally, the guidelines prescribed by the South African Medical Research Council on the Responsible Conduct of Research (South African Medical Research Council, 2018) were also adhered to.

3.2.3.1 Addressing Harm (non-maleficence)

In this study the collection of blood for testing could cause pain. This was explained to the patient. However, care was taken to avoid causing unnecessary pain to the patient.

3.2.3.2 Autonomy

Regarding the principle of autonomy, participation in research as a subject should be voluntary, without any coercion. The purpose and conduct of the study were fully and meaningfully explained to the potential participants. They were made aware of their right to refuse to participate without any prejudice to their care. Furthermore, they were informed that they were free to withdraw from the study at any time without having to explain or give any reason, and this would not compromise their treatment. The patients were then requested to sign the consent form if they voluntarily agreed to take part in the study.

3.2.3.3 Anonymity and confidentiality

The privacy and dignity of the patient were assured by anonymisation and removal of any identifying information from the data sheets before data transcription. This was done by the allocation of study subject numbers during data transcription, and removal of any potential personal identifiers. Patients' identifying details were only used to access the hospital files for the purpose of recording clinical information and did not appear in the final report, or in any publication that may arise from this study. Access to the data was restricted to the research team for research purposes and to health care practitioners directly involved in the clinical care of the patient. Hospital files were securely kept at the hospital records department. Raw physical data was kept securely by the researcher in a locked room when not in use, and electronic data was password protected.

3.2.3.4 Beneficence

In this research, the benefit that the patient might gain was that if any abnormalities were detected in their thyroid functions, they would be referred to the appropriate specialist for further management. In this research, the life and health of the patient were what guided the radiation therapy treatment for the patient's cancer and knowing whether the patient developed hypothyroidism was important because the treatment

would be offered if required. This would alleviate the symptoms of hypothyroidism that would otherwise reduce the quality of life.

Additionally, other patients undergoing head and neck radiotherapy would benefit by proactively investigating them for any adverse effect resulting from radiation to the thyroid gland during radiotherapy and the subsequent follow-up.

3.2.3.4 Ethical clearance

The commencement of the study took place after ethics approval from the Turfloop Research and Ethics Committee, approval number TREC/415/2017: PG dated 02 November 2017 (annexure D) and TREC/415/2017: PG-Renewed (Annexure E). Additionally, permission to carry out the study in the hospital was sought from the Limpopo Department of Health (annexure F). Approval was obtained from the Pietersburg/ Mankweng Research Ethics Committee as well (annexure G). Permission was also obtained from the Clinical Executive Director of Pietersburg Hospital as well as from the Head of Department of Radiation Oncology.

3.2.4 Data analysis

Data analysis was done with STATA version 16.0. Kruskal-Wallis test and Mann Whitney test were used to analyse the association between any change in thyroid function tests and the variables. Wilcoxon signed rank test was used to study the effect of radiation therapy on thyroid function. Descriptive statistics (means, proportions, frequency) were used to characterise the variables such as age, radiation dose, fT4 and TSH levels. A p-value of <0.05 was considered statistically significant. The details of results have been summarised in frequency tables, graphs and charts in the results section of this document (Chapter 4).

3.3 RELIABILITY AND VALIDITY

3.3.1 Reliability

Reliability refers to the consistency of the measure (Price, Chiang and Jhangiani, 2015). Reliability, specifically concerning the consistency of laboratory testing of the specimens, was addressed as follows: Blood samples were processed and analysed at the laboratory using a Beckman Access® immuno analyser which uses a 3rd generation chemiluminescent immunoassay system which is capable of detecting a lowest TSH of 0.003 mIU/mL hence considered accurate. Additionally, the researcher collected data from each patient in a systematic way using the same method each time. This enhanced the reliability and gave direction on how data collection can be repeated for a similar study in future.

3.3.2 Validity

Validity refers to the degree to which observed effects of an experiment can be attributed to the manipulated independent variables (Brink, Van der Walt and Van Rensburg, 2012). Two different types of validity are considered here. Internal validity is defined as extent to which the observed results represent the truth in the population studied and, thus, were not due to methodological error (Patino and Ferreira, 2018). In addressing internal validity in this study, all patients who satisfied the inclusion criteria were given equal chance to participate. Upon enrolment, specific enquiry was made into whether there was any known pre-existing thyroid condition for each subject. Secondly, the current medication use was documented to detect any that may potentially affect thyroid function. These were noted and if present patients were excluded. Thirdly, pre-treatment thyroid function assessments formed an accurate baseline for comparing subsequent thyroid function measurements. Lastly, patients with nasopharyngeal cancer were excluded from enrolling in the study. In nasopharyngeal cancer the radiation therapy portal generally encroaches on the hypothalamus, and thus places them at risk of secondary hypothyroidism due to hypofunction of the hypothalamus. Any observed fT4 and TSH changes in the study group would therefore be attributed to the effect of radiation on the thyroid gland itself.

External validity, relates to the extent to which the results can be generalised from the study sample to the general population (Frambach, Van der Vleuten and Durning, 2013). In this study external validity was ensured by using statistical methods to evaluate the relationship between the variables that may influence thyroid functions among the patients. It would be possible to generalise the result from this cohort of patients to any other patient with head and neck cancer receiving radiotherapy.

3.3.3 Bias

Bias is defined as a systematic error in a study that occurs rather than random variation or lack of precision (Sedgwick, 2014). To minimise the likelihood of bias, special attention was paid to specifically the recruitment, the measurement of outcomes, and the reporting of results.

Firstly, to ensure an unbiased recruitment process, all patients who presented to the department were eligible to enrol in the study by non-randomising the process. Bias was minimised during the measurement of outcomes by acquiring numerical data variables, and the application of statistical analysis to the data obtained. The results of all data are reported for all patients recruited in the study to ensure that all outcomes are consistent.

3.4 CONCLUSION

Details on sampling, data collection, and the data analysis process are presented. Included is a detailed section on considerations made to ensure validity and reliability. The over-arching principles of adherence to medical ethics codes guided the entire process.

CHAPTER FOUR

4. RESULTS

4.1 INTRODUCTION

This chapter describes data management and analysis, and presents the research findings. It is structured according to the objectives of the study, which were:

- To determine the prevalence of clinical hypothyroidism in head and neck cancer patients post radiation therapy at Pietersburg Hospital.
- To determine the prevalence of sub-clinical hypothyroidism in head and neck cancer patients post radiation therapy at Pietersburg Hospital.
- To investigate the relationship between the extent of hypothyroidism, radiation dose and the time of onset.

4.2 DISEASE AND DEMOGRAPHIC CHARACTERISTICS OF THE PATIENTS

A total of thirty-seven (37) patients were enrolled in the study. The characteristics of the patients with regard to age, site and stage of cancer are presented in Table 4.1.

Characteristic	
Sample size, n	37
Age, years (mean±SD)	53.1±12.3
Site (%)	
Oropharynx	18.9
Oral cavity	29.7
Larynx/Hypopharynx	29.7
Sinonasal	10.8
Others*	10.8
Cancer stage (%)	
Early	8.1
Moderately advanced	29.7
Locally advanced	62.2

*others: orbit, ear, Hodgkin's lymphoma

Table 4.1: Characteristics of patients

4.2.1 Distribution by sex

There were more males (n=26; 70%), than females (n=11; 30%).

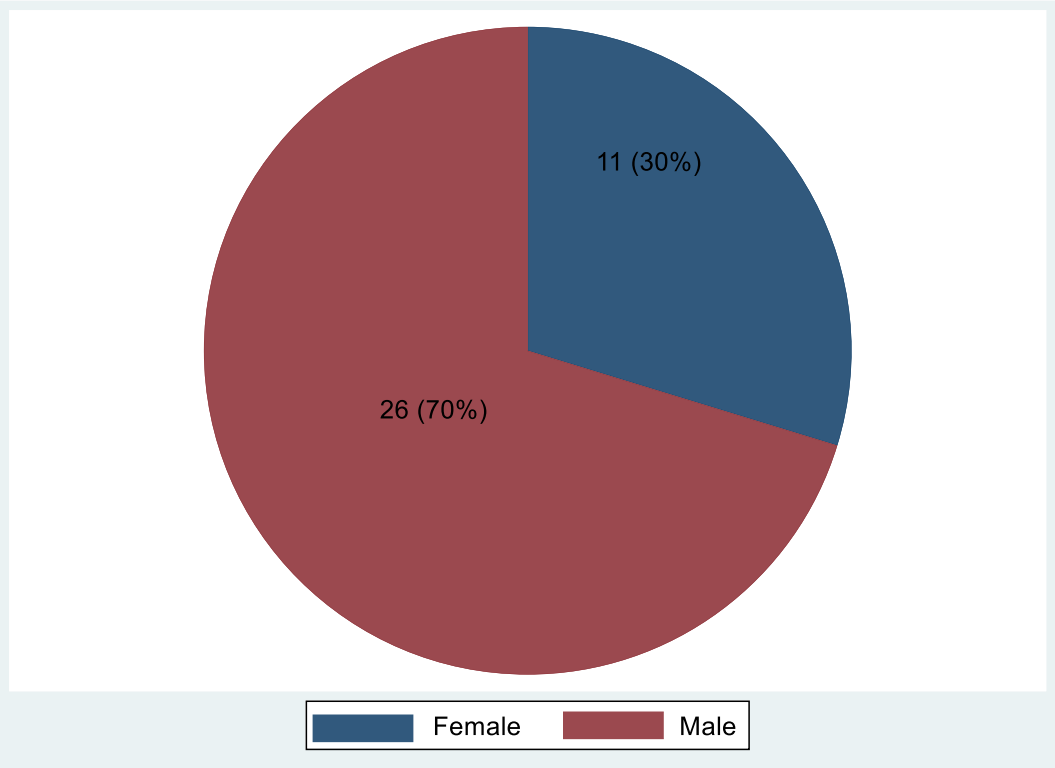


Figure 4.1: Patients according to sex

4.2.2 Distribution by age

The mean age of the patients was 53.1 years (53.1±12.3 Standard deviation [SD]) with a range of 40.8 to 65.4 years. Most of the patients (n=22; 59.4%) were 50 years old or older. The single largest age group was 50 to 60 years old, with 12 patients (32.4%). The second largest age group was of those older than 60 years of age (n= 10; 27%). Only 7 patients (18.9%) were in the age group of between 40 and 49 years old, and 8 patients (21.6%) were younger than 40 years of age (Figure 4.2).

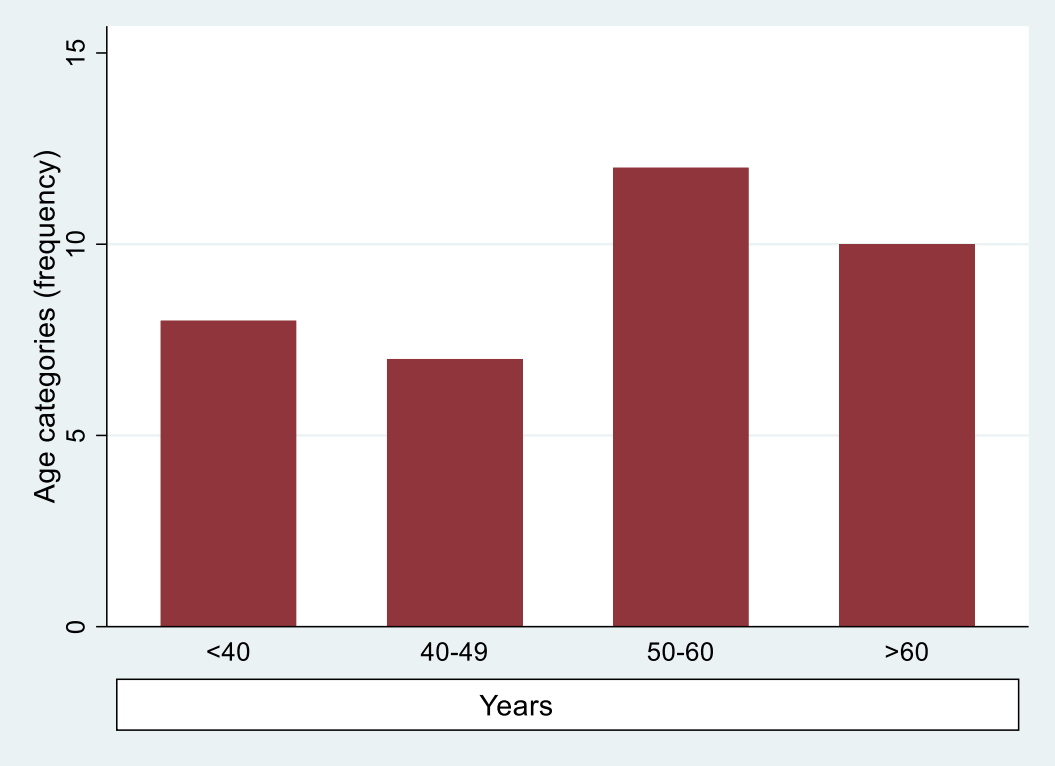


Figure 4.2: Patients according to age categories

4.2.3 Distribution by performance status

Most of the patients presented with an ECOG performance score of 2 (78%; n=29), while only 8 patients (22%) in the study had an ECOG score of 1. (Figure 4.3.)

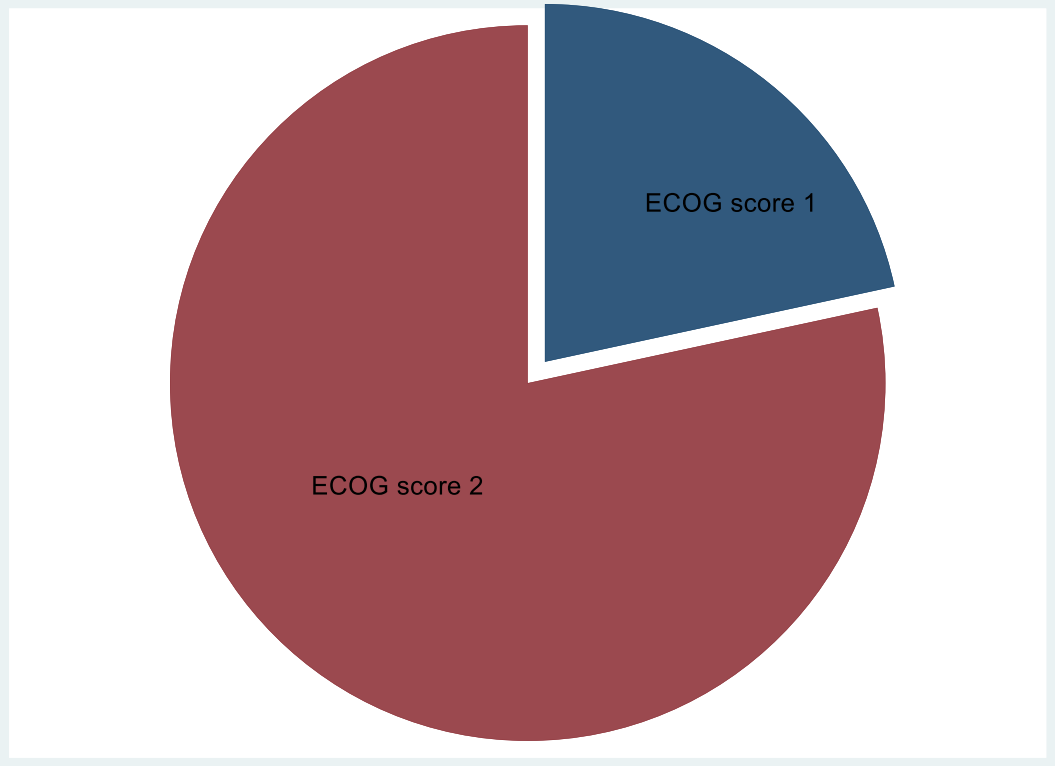


Figure 4.3: Patient's Performance score

4.2.4 Distribution by site of cancer

There were 11 patients (29.7%) with cancer of the larynx or hypopharynx 11 patients (29.7%) with cancer of the oral cavity, followed by oropharyngeal cancers (n=7; 19%), sinonasal sites (n=4; 11%), and malignancy in other sites (n=4; 11%). Malignancies from other sites comprised of 2 orbital tumours, 1 primary tumour of the ear, and 1 Hodgkin's lymphoma. The distribution according to site of the malignancy is presented in figure 4.4.

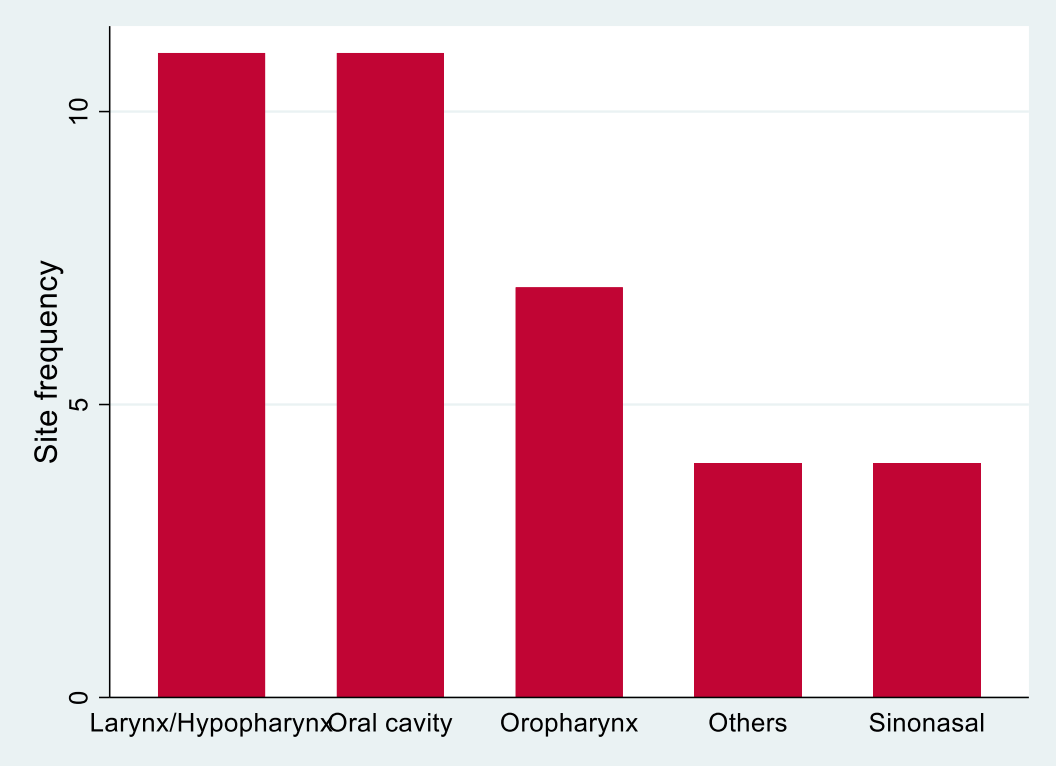


Figure 4.4: Cancer site frequency

4.2.5 Distribution by cancer stage

More than half of the patients (n=23; 62%) had a locally advanced cancer stage and only 3 (8%) had an early-stage cancer. Eleven patients (29.7%) had moderately advanced cancer (Figure 4.5).

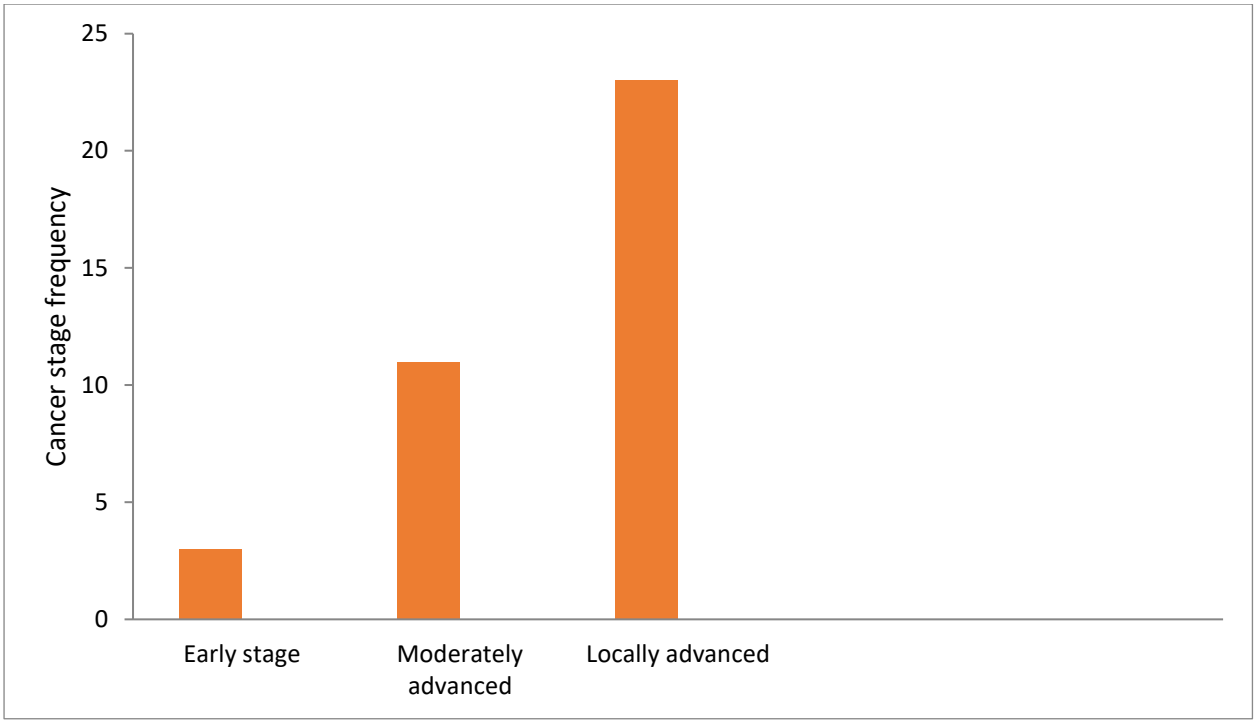


Figure 4.5: Cancer stage of patients.

4.2.6 Total dose of radiotherapy received

Twenty-eight patients (76%) received a total radiation dose of 70Gy to the head and neck region at 2Gy per fraction daily, treated 5 days per week on weekdays , over 7 weeks. Nine patients (24%) received less than 70Gy, at 2Gy or 3Gy per fraction daily, Monday to Friday, with a resting period on Saturday and Sunday, over 2 to 4 weeks. All patients completed their prescribed dose of radiotherapy. (Figure 4.6).

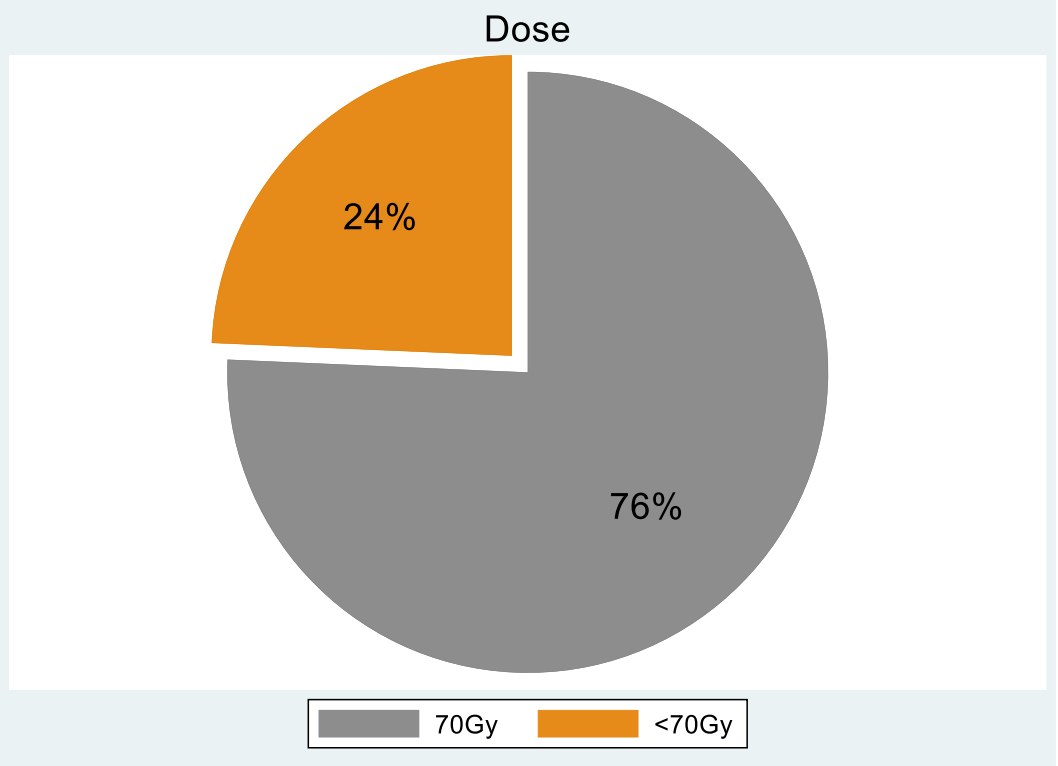


Figure 4.6: Total radiation dose

4.3 SYMPTOMS RELATED TO HYPOTHYROIDISM

The most common symptom after radiotherapy was fatigue, which was reported by 62% of patients. This was followed by cold intolerance (54% of patients) and weight gain and dry skin or dry hair (reported by 43% of patients each) (Figure 4.7).

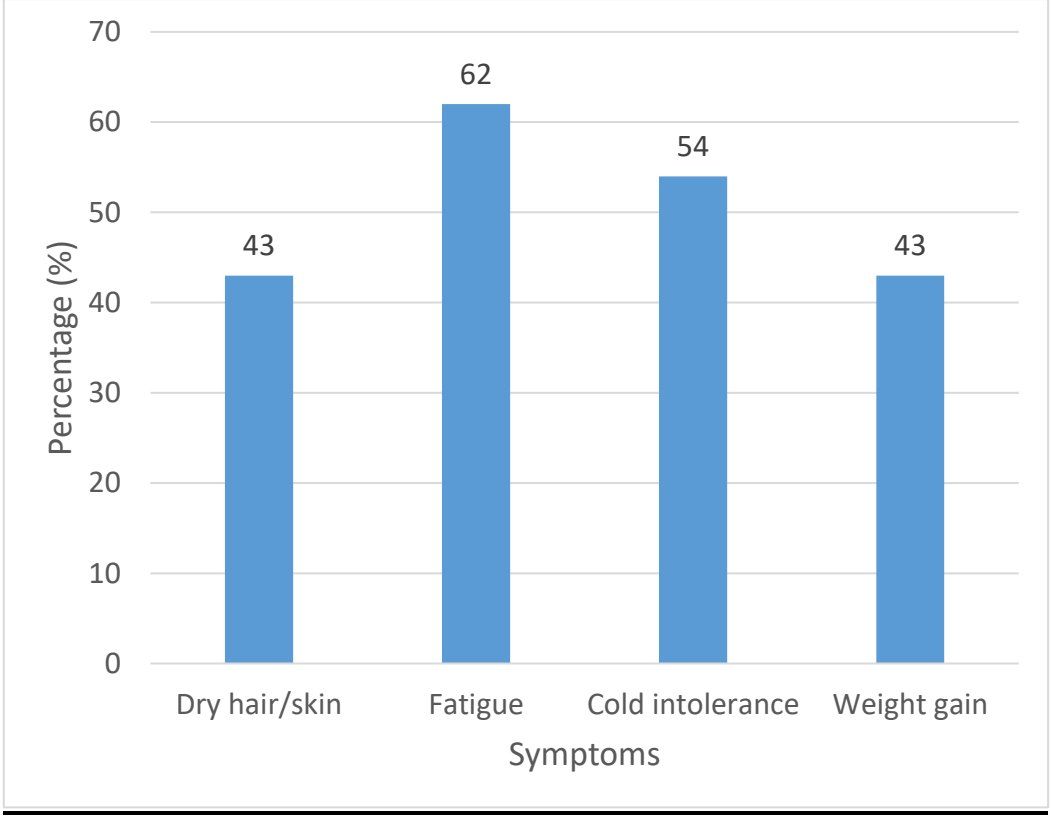


Figure 4.7: Patients' symptoms after radiation therapy

4.4 THYROID FUNCTION BEFORE AND AFTER RADIATION THERAPY

Of 37 patients, only 29 patients who had post radiation therapy blood tests for TSH and fT4 were included in the final analysis.

4.4.1 Correlation between change in TSH and change in fT4

There was no statistically significant increase in TSH (change of 0.1 [-0.5-0.8], p=0.99) or decrease in fT4 (change of -0.3 [-3.8-0.9], p=0.82) after radiation therapy (Table 4.2).

Thyroid function	Pre- RT (n=37)	Post- RT (n=29)	p-value (Wilcoxon signed- rank test)
TSH (mIU/L), median [IQR]	1.2 [0.85-2.1]	1.3 [0.70-1.93]	0.99
fT4 (pmol/L), median [IQR]	12.7 [10.5-14.35]	11.1 [10.0-12.4]	0.82
Percentage of TSH change (%)^	8.33 [-48- 46.9]		
Percentage of fT4 change (%)#	-2.05 [-26.6-9.24]		

^percentage of TSH change= change in TSH/pre TSH x 100;
#percentage of fT4 change= change in fT4/pre fT4 x 100;

Table 4.2: Effect of radiation on thyroid function on TSH and fT4 patient serum concentration

4.4.2 Prevalence of subclinical and clinical hypothyroidism

None of the patients developed clinical hypothyroidism post-radiotherapy. Only 2 (6.8%) patients developed subclinical hypothyroidism post-radiotherapy, manifesting as raised TSH levels above the upper normal limit. (Figure 4.8 and 4.9).

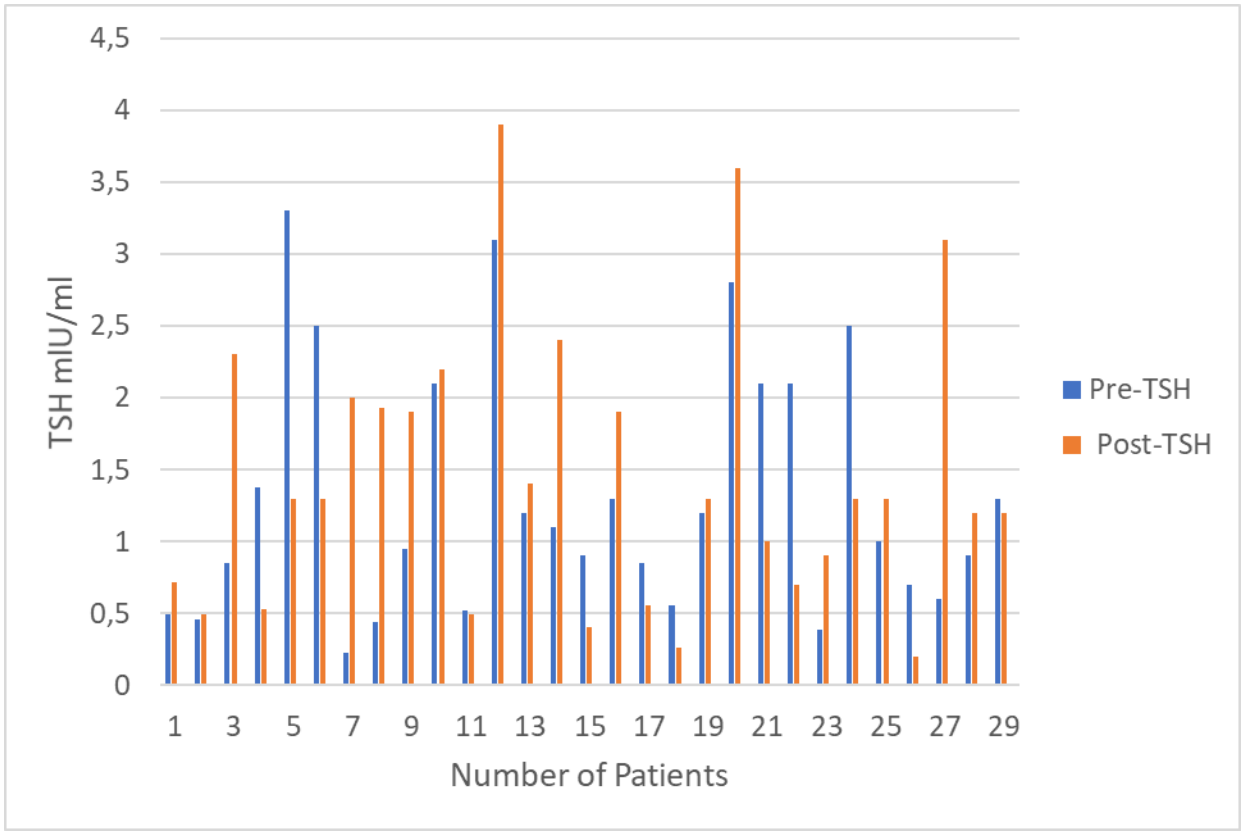


Figure 4.8: TSH serum concentration pre and post radiotherapy

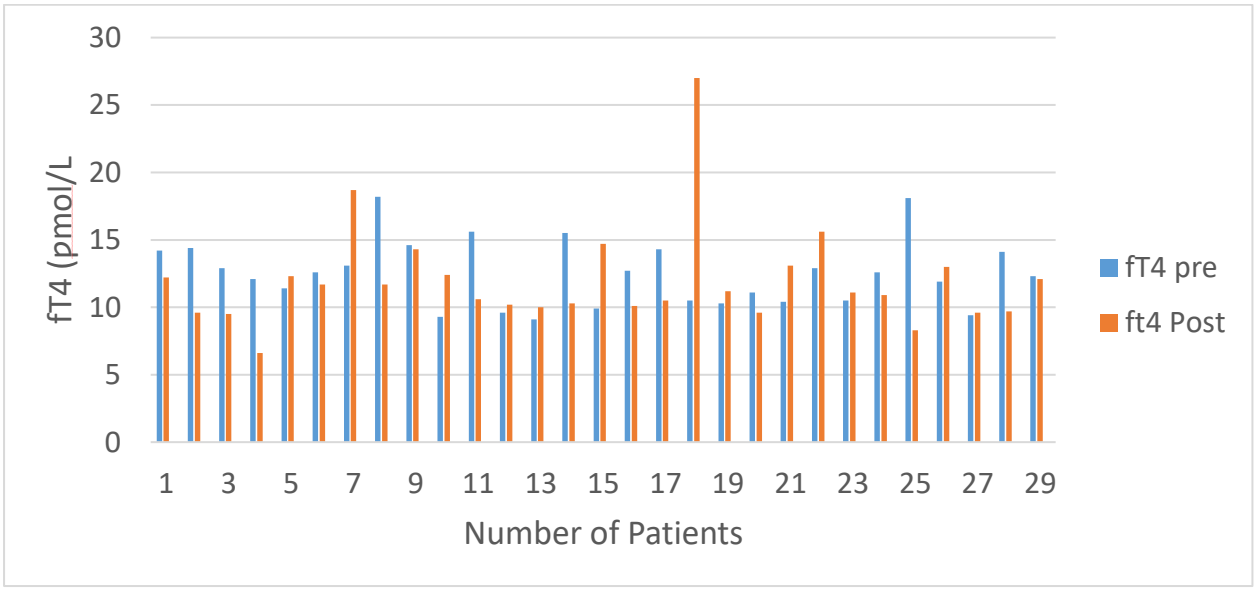


Figure 4.9: fT4 serum concentration pre and post radiotherapy

4.5 ASSOCIATIONS BETWEEN CHANGE IN THYROID FUNCTION AND PATIENT CHARACTERISTICS, AND OUTCOMES SYMPTOMS

No statistically significant associations were found among the change in TSH and fT4 when comparing to the baseline patient characteristics and their symptoms post radiotherapy. See Table 4.3.

Thyroid function n=29	p-value of TSH change vs.	p-value of fT4 change vs.
Sex	0.55	0.15
Performance score	0.76	0.84
Site#	0.17	0.74
Stage*	0.21	0.78
Dose	0.99	0.79
Dry skin/hair	0.97	0.15
Fatigue	0.33	0.42
Cold intolerance	0.80	0.43
Weight gain	0.82	0.25

*Stage was collapsed to 2 categories for the association analysis, # Kruskal-Wallis test performed only for site, for the remaining variables a Mann-Whitney test was used.

Table 4.3: Effect of radiation therapy on thyroid function on TSH and fT4 patient serum concentration

There was no statistically significant correlation between changes in TSH and fT4 vs. age (r= 0.02, p=0.88 and r= 0.03, p=0.92) respectively. See Figure 4.10 and Figure 4.11.

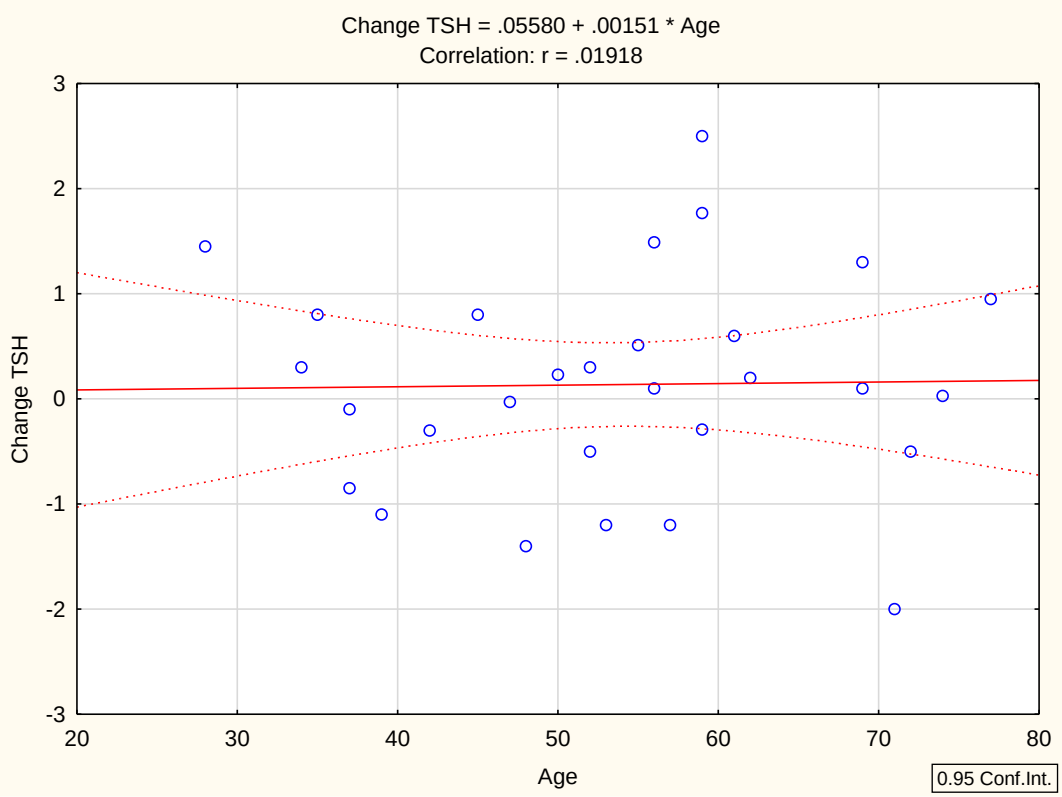
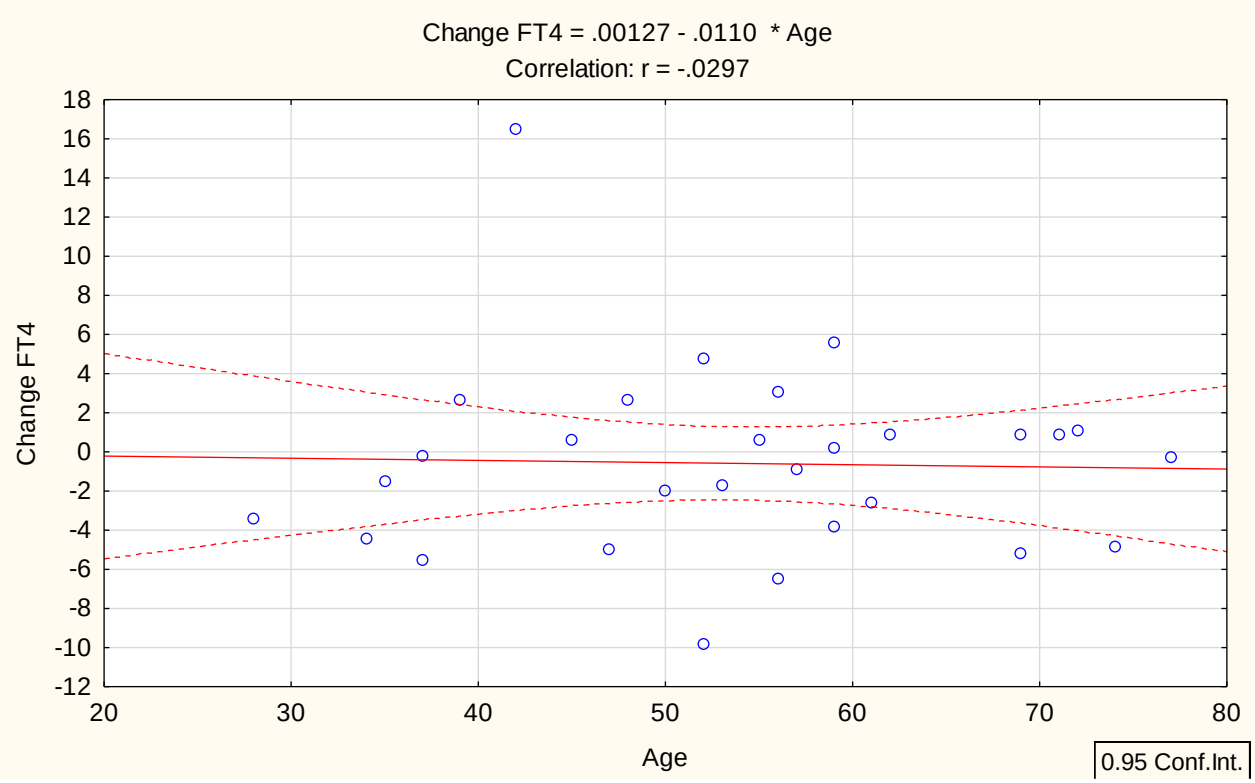


Figure 4.10. Correlation between changes in TSH vs age.



Figures 4.11. Correlation between changes in fT4 vs age.

4.6 CONCLUSION

No statistically significant change in thyroid function tests post-radiotherapy was found compared to pre-radiotherapy.

CHAPTER FIVE

5. DISCUSSION

5.1 INTRODUCTION

Having presented the results of the research in the last chapter, this chapter now interprets and discusses the results. The findings are interpreted and discussed with reference to the objectives of the study and compared to the results from similar studies found in the literature. The limitations of the study are highlighted and the significance of the findings oncology are presented.

5.2 RESEARCH DESIGN AND METHODOLOGY

A prospective (cohort) observational study was carried out. In this study patients with head and neck cancers treated with radiotherapy for their cancers were observed for the effect of radiotherapy on thyroid gland functions since the thyroid gland is inadvertently included in the radiotherapy field. The study was conducted at the radiation oncology department in the Pietersburg Hospital. The hospital is an academic hospital affiliated to the Faculty of Health Sciences in the University of Limpopo. Blood tests for thyroid function were performed at the start of radiation therapy. The tests were repeated on the first day of follow up, 6 weeks after radiation therapy, and the patient interviewed for the presence of any symptoms of hypothyroidism such as dry skin, dry hair, fatigue, cold intolerance, or weight gain.
Sample size (n=37) was calculated using a paired t-test in Statistica programme V13.0, was based on a 15% reduction in fT4 levels from a mean of fT4=12.8 30 days after radiotherapy with a power of 80% and a significance level of 5% (reduction of 23.5% of fT4 after 30 month of radiation therapy (Lin *et al.,* 2018).

5.3 SUMMARY OF THE RESEARCH FINDINGS

5.3.1 Definition of hypothyroidism.

The definition of hypothyroidism varies significantly between different authors regarding the reference ranges for TSH and fT4 levels. This is crucial when the findings are based on the deviation from a reference point specified in each study. Zhou *et al.,* (2021) notes this in a review article and comments that the diversity in the definitions of hypothyroidism means that there will be differences in the interpretations of the values of TSH and fT4 (Zhou *et al.*, 2021).

According to Haarburger (2012) the reference range for TSH has become controversial. Haarburger goes on to explain that although the lower limit for TSH of 0.3mIU/L is generally agreed upon, the upper limit of normal, however, has become contentious, with some using 2.1mIU/L, and others defining the upper limit to be 7.5mIU/L. The author also highlights that the differing sensitives for different isoforms of TSH in different assays can in themselves result in a rise of upto 1.0mIU/L (Haarburger, 2012). The reference range for the TSH levels in the present study was defined according to the American Thyroid Association Recommendations (Garber *et al.*, 2012). These specify normal TSH range in adults as between 0.39-3.55 mIU/L. The reference range for fT4 values used is between 7.6 – 16.1pmol/L.

In primary hypothyroidism, decreased production of thyroid hormones by the thyroid gland causes a compensatory increase of TSH (Shahid *et al.*, 2018). Cases showing elevated TSH levels (>3.5 mIU/L) and decreased fT4 levels, with clinical symptoms are classified as clinical hypothyroidism, whereas those with elevated TSH levels (>3.5mIU/ml) and normal T4 values are classified as subclinical hypothyroidism. Results falling within the reference ranges for both TSH and fT4 tests were considered normal/euthyroid. In South Africa a similar reference range of 0.35-3.5mIU/L for TSH, and 7.6-16.1pmol/L for fT4 is recommended (Du Plessis, Rossouw, Van Niekerk and Van der Watt, 2016). Accordingly, in the present study cases showing elevated TSH levels (>3.5 mIU/L) and decreased fT4 levels, with clinical symptoms are classified as clinical hypothyroidism, whereas those with elevated TSH levels (>3.5mIU/ml) and

normal T4 values are classified as subclinical hypothyroidism. The results falling within the reference ranges for both TSH and fT4 tests are considered a normal or euthyroid state.

Ronjom, *et al.* (2015a) conducted research on external validation of a normal tissue complication probability model for radiation-induced hypothyroidism and find that there is a significant correlation between the pre-treatment TSH value and thyroid gland size: Patients with a smaller thyroid gland size had higher pre-treatment TSH values. In that study they used the pre-treatment TSH value > 4.0 mIU/L, to define hypothyroidism for the first time. The same author conducted a follow-up study which evaluated the increase in TSH from baseline of change in TSH > 2.7 mIU/l. This threshold change was chosen so that the number of patients with hypothyroidism was identical to the number achieved based on an absolute TSH level above 4 mIU/l in the study. The results obtained using the external validation group show that the pre-treatment TSH value is closely related to hypothyroidism (Rønjom *et al.*, 2015b).

5.3.2 Symptoms of hypothyroidism.

In the present study the most common symptom after radiotherapy was fatigue (62%), followed by cold intolerance (54%), and weight gain and dry skin/hair (43% each) [See figure 4.7]. Similar finding of clinical symptoms of hypothyroidism such as fatigue, drowsiness, intolerance to cold, weight gain, constipation, aural changes, and dry skin in post radiotherapy in head and neck cancer patients are reported elsewhere (Carlé, Bülow Pedersen Knudsen, Perrild, Ovesen and Laurberg, 2015).

5.3.3 Post radiotherapy clinical hypothyroidism in head and neck cancer patients

Out of the 37 patients who participated in the present study, none of them developed clinical hypothyroidism by the time of last review. Only one patient had a low fT4 level (6.6pmol/L), but with normal TSH levels. Overall, fT4 levels changed by -2.05% after radiation therapy compared to the baseline levels. However, the decrease in fT4 level is not statistically significant. Similarly, the observed increase in mean TSH (change

of +0.1mIU/ml [-0.5-0.8]) after radiation therapy was also not statistically significant (p=0.99).

A retrospective study involving 1 116 head and neck patients finds an overall incidence of clinical hypothyroidism to be 6.5% after radiation therapy (Khurram *et al.*, 2014). The prevalence of post radiation therapy hypothyroidism in this study (6.5%) was however lower than that found in most other studies. Similarly, two other studies, also find that the incidence of clinical hypothyroidism (elevated TSH level and depressed fT4 level) varies from 5 to 10% (Tami, Gomez, Parker, Gupta and Frassica, 1992; Vrabec and Heffron,1981).

However, other studies report a much higher prevalence of post radiotherapy hypothyroidism. A study of 128 patients who received radiation therapy and followed-up every 3 to 6 months for up to 3 years with TSH testing found that 61 patients (47.7%) developed hypothyroidism by the end of the study period, hypothyroidism occurring at a median of just 1.08 years after radiation. The authors also find the earliest detectable case of hypothyroidism occurred as early as 2.9 months (Diaz, Jaboin, Morales-Paliza, Koehler, Phillips, Stintson, Gilbert, Chung, Murphy, Yarbrough, Murphy, Shyr and Cmelak, 2010).

A recent prospective single arm study of 78 patients conducted over 3 years finds that the incidence of hypothyroidism rose over time after radiation therapy (El-Shebiney *et al.*, 2018). Baseline thyroid functions were assessed followed by repeat assessments at all scheduled follow-ups. In this study it is found that the median cumulative incidence of hypothyroidism was 24.6%, 36.5% and 42.3% at one, two and three years respectively. In absolute numbers, out of the 78 patients, 33 had developed hypothyroidism by 37 months. Importantly, 27 out of these 33 had overt/clinical hypothyroidism. El-Shebiney *et al.* (2018) show the development of hypothyroidism after a median 31 months of follow-up duration (range 18–37 months), and that the incidence of hypothyroidism increased with time.

5.3.4 Post radiotherapy sub-clinical hypothyroidism in head and neck cancer patients.

In the present study, only 2 patients (6.8%) were found to have developed sub-clinical hypothyroidism, with post radiotherapy TSH values above 3.5mIU/ml. These findings are consistent with other studies despite the wide variation of the definition of subclinical hypothyroidism in the different studies.

In the Egyptian study cited above, El-Shebiney *et al*. (2018) report that 33 patients (42.3%) developed hypothyroidism by 37 months, 27 of these had clinical hypothyroidism, and the remaining 6 (7.7%) had subclinical hypothyroidism. Liening, Duncan, Blakeslee and Smith (1990) conducted a retrospective study in 96 patients and find the prevalence of clinical hypothyroidism to be 26% and that of sub-clinical hypothyroidism to be 6%. This is in contrast to Turner and Jones (2008) who find a 14.3% incidence of clinical and 23.8% sub-clinical hypothyroidism following radiotherapy to the thyroid gland.

5.3.5 The relationship between hypothyroidism, radiation dose and the time of onset.

In the present study the correlation between changes in TSH and fT4 to radiation doses were not statistically significant (p-value of 0.99 and 0.79, respectively). In spite of lack of statistical significance, it is important to note that two patients who each received a total dose of 39Gy in daily fractions of 3Gy per fraction developed sub-clinical hypothyroidism with TSH values above 3.5mIU/ml after radiotherapy at 3 months.

Nearly two decades ago, a landmark publication predicted that the 5-year risk of thyroid dysfunction is 5% with a 45-Gy dose and 50% with an 80-Gy dose (Emami *et al.*, 1991). This is consistent with the findings of a study by Kuten, Lubochitski, Fishman, Dale and Stein (1996) who find that the total dose of irradiation is the most important factor associated with an increased incidence of subsequent hypothyroidism.

Many other researchers also detected thyroid dysfunction at total doses ranging from 32Gy to 45Gy. Kim, Yu and Wu (2014) retrospectively analysed 114 patients with head and neck cancer and show that if more than half of the thyroid gland is exposed to a 45Gy dose, it became an independent predictor of developing hypothyroidism ($p = 0.024$). The 1-year cumulative incidences of hypothyroidism in the patients in whom more than half of the thyroid gland received 45Gy or more was 56.1% and those in whom half of the thyroid gland received less that 45Gy had an incidence of 22.8% (Kim *et al*., 2014). Similarly, Yazdani *et al.* (2019) find that a mean thyroid dose of 32 Gy caused functional abnormalities of the gland. Murthy, Narang, Ghosh-Laskar, Gupta, Budrukkar and Agrawal (2014) conducted a study in which 44 patients with head and neck cancer who received radiotherapy and find that a thyroid dose less than 40Gy could reduce the incidence of hypothyroidism. Another study also found that the incidence of hypothyroidism increased with mean thyroid gland radiation dose. In this study, the hypothyroidism probability increased with higher mean thyroid gland dose ($P<0.001$), with an odds ratio of 1.064/Gy (95% CI 1.029-1.101) (Boomsma, Bijl, Christianen, Beetz, Chouvalova, Steenbakkers, van der Laan, Wolffenbuttel, Oosting, Schilstra and Langendijk, 2012).

In the last 10 years, several researchers have attempted to explore the concept of a dose threshold for the thyroid gland. Fujiwara, Kamikonya, Odawara, Suzuki, Niwa, Takada, Doi, Terada, Uwa, Sagawa and Hirota (2015) suggest from their study's findings that the most important independent predictor of thyroid hypofunction is the mean dose the thyroid gland received, and that a total dose <30Gy could protect the thyroid gland. In a retrospective evaluation of data from 75 consecutive head and neck cancer patients who received radiotherapy with median dose 66Gy, it was found that both acute and late effects on the thyroid gland were evident after radiation doses between 30Gy up to 70Gy (Fujiwara *et al*., 2012). Patients who received a mean thyroid dose less than 30Gy had significantly lower incidence of hypothyroidism (Fujiwara *et al*., 2012).

Most of the studies cited had only a single arm of patients who received radiotherapy to the head and neck region. A study by Chougule and Kochar (2011) enrolled 90 patients who received radiotherapy in the treatment arm and a matched group of

healthy individuals in the control arm. The treatment arm had thyroid function testing at baseline and repeated midway through radiotherapy and again upon completion of the radiotherapy (dose range 60 to 70Gy). Thyroid tests were repeated at 3 and 6 months post-radiotherapy. They find a statistically significant decrease in mean fT4 levels during radiotherapy and at 6 months follow up compared to fT4 levels before treatment ($p<0.005$). A non-significant increase in TSH was found with mean TSH of 2.01mIU/ml at the completion of therapy and mean TSH of 3.69mIU/ml at 6 months after radiotherapy compared to the control group, the p-value was not specified (but was reported as non-significant) (Chougule and Kochar, 2011).

When looking at the short-term relationship between time and TSH change a study by Kim *et al*. (2014) interestingly postulate that the elevation of TSH after radiation therapy may be a temporary phenomenon and that TSH may return to its normal level over time. They felt that this could lead to short term high false positive rates. In their study, 46% of the patients were diagnosed as hypothyroid after a median time of 8 months (range 1–24). They acknowledged that this relatively high incidence over a short period supports the importance of long-term follow-up duration to estimate the true incidence of radiation-induced hypothyroidism. However, they find no spontaneous recovery of TSH in these patients after a follow-up of up to 38 months (Kim *et al.,* 2014).

Alkan, Baylancicek, Çiftçic, Sozen and Dadaş (2008) report average time to detection of hypothyroidism of 6 months after the completion of radiotherapy. Similar findings are made by Miyawaki, Yoshida, Ejima, Nishimura, Sulaiman, Kiyota, Saito, Otsuki, Nibu and Sasaki (2013) who studied thyroid function in 130 patients with head and neck cancers treated with conformal radiotherapy. All patients received primary radiotherapy of between 60-70.8Gy in 30-36 fractions. Hypothyroidism occurred in 57 patients (56.2%). Thirty-one patients of these (54.4%) had clinical hypothyroidism and required replacement therapy. They found hypothyroidism developed after a median interval of 11 months (range, 2-50 months) and increased over time in contrast to Kim *et al.* (2014) who analysed thyroid function in 114 patients at 1 month, and repeated at 6 months, 1 year and 2 years after being treated with radiotherapy. The cumulative risk of hypothyroidism in all patients after 1, 2 and 3 years of irradiation was 3.2%, 14.3% and 33.5%, respectively (Miyawaki *et al*., 2013).

Several other researchers, however, find that it took much longer to detect any sub-clinical hypothyroidism in their studies. Colevas, Read, Thornhill, Adak, Tishler and Busse (2001) find the peak incidence of occurrence of radiation-induced hypothyroidism at 2 to 3 years post radiotherapy. While using a more precise modality of delivering radiotherapy as compared to 3D-CRT, Chyan, Chen, Lambert, Quivey, Shugard and Yom (2014) conducted a retrospective study of oropharyngeal cancer patients treated with intensity modulated radiation therapy (IMRT). They record after a median follow up of 4.6 years, hypothyroidism in 61% of patients and the peak incidence of hypothyroidism occurred within the first 3 years after treatment.

Garcia-Serra, Amdur, Morris, Mazzaferri and Mendenhall (2005) performed a large retrospective study of 504 patients with head and neck cancer whose radiation therapy fields included the thyroid gland. Of the 504 total patients, 206 had a serum TSH level checked at some point posttreatment. Of the 206 patients who had a documented post-treatment TSH, it was found that the actuarial freedom from hypothyroidism was 58% at 5 years and 26% at 10 years. Garcia-Serra *et al.* (2005) thus conclude that head and neck irradiation results in biochemical hypothyroidism in at least 50% of patients and advised that thyroid function should be tested on a regular basis following radiotherapy to the low-neck region. Based on their findings, they recommend that TSH level should be assessed every 6 months during the first 5 years after radiotherapy, and thereafter annually (Garcia-Serra *et al.,* 2005).

5.4 THE RELATIONSHIP BETWEEN HYPOTHYROIDISM AND OTHER CLINICAL FACTORS

5.4.1 The relationship between hypothyroidism and age.

In the current study, the mean age of patients was 53.1 years. 59% of the patients were over 50 years (range 28 - 77). There was no statistically significant correlation between changes in TSH and fT4 vs age ($r= 0.02$, $p=0.88$ and $r= -0.03$, $p=0.92$ respectively). Of the two patients who developed subclinical hypothyroidism one was 45 and the other was 55 years old.

Most of the studies had a similar age group range to that in the present study.

The relationship between age and risk of subsequent hypothyroidism after radiation therapy is also an area of inconsistency. Some studies find age to not be associated, while others find a younger age group to be at higher risk, and still others find older people to be at higher risk.

Banipal *et al.* (2011) conducted a prospective study which had 53 patients with a mean age of 55.9 years (range 30-75 years) with head and neck cancers. They find subclinical hypothyroidism in 4 (7.5%) of the 53 patients. Of the 4 patients, 3 were of age ≤41 years and 1 was 66 years. They find that patients of younger age group (30-39 years), had a TSH which showed a statistically significant ($P < 0.05$) increase in TSH values.

Tell *et al.* (2004) had an older median age of patients in their study (65 years old) and find that older age increased the risk of subclinical hypothyroidism but did not affect the incidence of clinical hypothyroidism. In the present study, age was not significant and the mean age of patients was 53 years.

Huang, Tan, Guo, Zhang, Peng, Peng, Lin, Mao, Sun, Ma and Tang (2019) contradict that finding in their large study of 345 patients as they note that a younger age (≤ 44 years old) is associated with hypothyroidism, although age was not significantly associated in the multivariate analysis. Of note, is that Huang *et al.* (2019), conducted their study retrospectively. Similarly, Diaz *et al*. (2010) find that the incidence of hypothyroidism decreased by 4% with every year increase in age. Thus, a patient 1 year older than another patient developed hypothyroidism at 0.96 times the rate of the younger patient (95% CI, 0.92–0.99). Diaz *et al.* (2010) enrolled 168 patients who received chemo-radiotherapy of which 61 of these were evaluable. The use concurrent chemotherapy and radiotherapy may have had an influence in their findings. In the present study chemotherapy was not administered. Thus, no conclusion on any relationship that might exist is considered.

In their research El-Shebiney *et al.* (2018) had patients with a mean age 60.54 years. Those that were euthyroid, had a mean age of 60.2 and those with hypothyroidism

had a mean age of 60.9 years. They conclude that age was not a statistically significant risk factor for development of post-radiation therapy hypothyroidism, with p-value = 0.731 (El-Shebiney *et al.,* 2018).

5.4.2 The relationship between hypothyroidism and sex.

In the present study, 70% of the patients were male and 30% were female. Both of the patients who developed subclinical hypothyroidism in the study were male. Further, the association between sex and TSH and fT4 change had p-value = 0.55 and 0.15 respectively. Both were not statistically significant. This is in keeping with the findings of a several other studies. Diaz *et al.*, (2010) finds that sex was not significantly related to risk of developing hypothyroidism (p = 0.15). This is a similar finding to Grande (1992) who conducted a multivariate analysis of risk factors and reports that there was no association between sex and subsequent risk of post-radiation therapy hypothyroidism. Ozawa, Saitou, Mizutari, Takata and Ogawa (2007) also studied 35 patients who had undergone neck radiotherapy for head and neck cancer and reported a non-significant finding of hypothyroidism in 13 of them (37%). In another study by El-Shebiney *et al.* (2018), the overall male to female composition of the euthyroid group post radiotherapy was 55.6%:44.4% versus the hypothyroid group of 54.5%:45.5%, being statistically not significant (p = 0.767).

Contrariwise, one study report a relationship between sex and risk of thyroid dysfunction after radiotherapy. In the study by Khurram *et al.* (2014) out of 1 116 patients, 341 were females and 775 were males. Of the 72 patients (6.45%) who developed hypothyroidism, 32 were female (9.4% of female participants) and 40 were male (5.2% of male participants). On univariate analysis, gender was the strongest predictor as hypothyroid patients were 1.90 (95% CI 1.17 - 3.09) times more likely to be females than males (p=0.008).

5.4.3 The relationship between hypothyroidism and stage of disease

In the present study, only 3 patients (8%) had an early-stage cancer (Stages 1 and 2), 11 Patients (29.7%) had a moderately advanced cancer (Stage 3) and most of the

patients 23 (62%) had a locally advanced cancer stage (Stage 4) with cervical lymph node involvement. There is no statistically significant association between the change in TSH and fT4 and the cancer stage (p = 0.21 and p = 0.78, respectively). No association is also found between hypothyroidism and type or stage of cancer (Kruskal-Wallis test: p–value = 0.17 and 0.74 for change in TSH and fT4, respectively). This finding is not consistent with some in the literature. Fujiwara *et al*. (2012) find that the incidence of hypothyroidism was significantly higher in patients with a positive cervical lymph node. Murthy *et al.* (2014) posit that head and neck cancer with positive lymph nodes may necessitate using a higher radiation dose to the neck thus increases the radiation exposure volume and the risk of thyroid irradiation, thus, positive lymph node status is an important risk factor for post radiotherapy hypothyroidism. This is plausible, as the total radiation dose is higher (60Gy in Pietersburg Hospital) when treating known nodal metastases, compared to 50Gy when the nodal region is treated electively. Some authors believe that special attention should be paid to patients with advanced nodal disease with individualised follow up of thyroid function test (Zhou *et al.*, 2021).

5.5 CONCLUSIONS OF RESEARCH FINDINGS

The present study did not find a statistical significant correlation between the factors studied and the risk of developing hypothyroidism following radiation therapy to the head and neck. It nevertheless demonstrates an increase in the mean TSH value, and a decrease in the mean fT4 levels within 3 months after radiation therapy, both of which suggest that radiation therapy to the head and neck may result in hypothyroidism. Only two patients developed sub-clinical hypothyroidism.

5.6 RECOMMENDATIONS

Although the findings in this study fail to reach statistical significance, they indicate the need for future research involving collaboration between multiple centres on a larger scale. A larger sample size would allow more accurate estimation of the possible adverse effect of radiation therapy on the thyroid gland and its magnitude.

Thus, a subsequent prospective study using a larger sample size with a longer follow-up duration should be carried out to better estimate the true extent of radiation induced hypothyroidism.

5.7 CONTRIBUTIONS OF THE STUDY

The short duration of the study with the lack of statistically significant findings, indicates there may be no value in monitoring thyroid function within the first 3 months after starting radiotherapy. This will reduce unnecessary thyroid function testing and associated costs at the first review after radiotherapy. It also indicates the need for longer-term follow-up of thyroid function in these patients.

5.8 LIMITATIONS OF THE STUDY

5.8.1 Sample size

The relatively small sample size in the study might have decreased the probability of detecting the true reflection of hypothyroidism in these patients. Further, when patients were lost to follow-up, the number of evaluable patients diminished and hence the accuracy and truthfulness of the findings.

5.8.2 Study duration

The follow-up duration may not have been long enough to detect late occurring hypothyroidism.

5.9 CONCLUSION

The result demonstrates a mean increase in TSH and a mean decrease in fT4 over the period of study which may suggest an evolving state of hypothyroidism. The limitations of this study were the short duration of follow-up and the relatively small number of participants. The recommendations from the study include the potential need for longer follow-up and monitoring of thyroid function tests in head and neck

cancer patients to preclude overlooked hypothyroidism as a late occurring radiation toxicity.

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ANNEXURE A: DATA COLLECTION SHEET

Title: Post radiation therapy hypothyroidism in patients with head and neck cancer at Pietersburg Hospital, Limpopo Province, South Africa.

Patients Research Identity number: _____

Section A: Patients Details

1. Name: _____Hospital Number: _____
2. Date of Birth: _____Age: _____years
3. Sex: _____
4. Contact details: Cell phone _____N
5. Physical address:

   _____

   _____

Section B: Research Data

1. Disease Site: _____
2. TNM Group Stage: __1____2_____3_____4_____
3. ECOG Performance Status: __1____2_____3_____4_____
4. Prescribed Radiation dose (Gy): _____
5. Dose per fraction (Gy): _____
6. Pre-existing known thyroid disease: _____YES/NO_____
7. Current Medication use: _____

Section C: Clinical Findings

Symptoms	Post-radiotherapy	
	Date	
	Yes/Present	No/Absent
Dry Skin		
Dry Hair		

Fatigue		
Cold Intolerance		
Weight gain		

Section D: Thyroid Function Assessments

	Pre-radiotherapy	Post Radiotherapy
	Date	Date
TSH Value (mIU/L)		
fT4 Value (pmol/L)		

ANNEXURE B: PARTICIPANT INFORMATION LEAFLET

Title of the research project:

Hypothyroidism after radiotherapy for patients with head and neck cancer at Pietersburg Hospital, Limpopo Province, South Africa

Reference number:

Principal investigator: Dr T J D Manavalan

Supervisor: Dr FO Ooko

Address:

Department of Radiation Oncology, Pietersburg Provincial Hospital, Polokwane, Limpopo.

Contact number: 015 287 5440

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is entirely voluntary, and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part, but change your mind later.

This study has been approved by the Turfloop Research and Ethics Committee and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

The study will be conducted at Pietersburg Provincial Hospital and will include several other patients who receive radiation therapy for cancer to the head and neck area.

The thyroid gland is a gland that is important for making hormones that help many functions take place. The Thyroid gland is positioned at the front of your neck, and so it could be damaged when you receive radiation. We want to check for this.

Before, during and after radiotherapy, when the other normal blood tests are done, we will also request a Thyroid Hormone level on this same sample.

All patients who receive radiation to the head and neck area will be offered the choice of participating in the study while it is running.

If it is found that your thyroid hormone levels are abnormal, a tablet to treat this may be offered to you.

Why have you been invited to participate?

All the patients coming to the department with head and neck cancers, who will receive radiation therapy to the head and neck area, will be offered the chance to participate.

What will your responsibilities be?

It is important that if you are on any treatment already for your thyroid or any other usual medication, you must tell us. It is also important that you do not miss your follow-ups as this will make the blood tests irregular.

Will you benefit from taking part in this research?

If your levels of the thyroid hormones are found to be abnormal, you would be given the treatment according to the national recommendations.

The results of this study could also help other patients in future with picking up and treating similar problems earlier.

Are there any risks involved in your taking part in this research?

No. There are no risks involved, as the management plan for your cancer will not be affected or altered in any way.

If you do not agree to take part, what alternatives do you have?

If you choose not to take part, you will still continue with all your other treatment (i.e., radiation and chemotherapy etc.) as was planned.

Who will have access to your medical records?

All the information collected will be treated as confidential and protected. If it is used in a publication or thesis, your identity will remain anonymous. The only people who will have access to your information are those involved in your care directly.

Will you be paid to take part in the study?

No, you will not be paid to participate in the study. There will be no extra costs or extra visits for you if you decide to take part.

Is there anything else that you should know or do?

You should inform your family practitioner or usual doctor when you come for check-ups that you are taking part in a research study.

You can contact Dr T.J.D. Manavalan at telephone 015 287 5440 if you have any further queries or encounter any problems.

You can contact the Turfloop Research and Ethics Committee at 015 268 2401 if you have any concerns or complaints that have not been adequately addressed by your study doctor.

You will receive a copy of this information and consent form for your own records.

ANNEXURE C: CONSENT

Declaration by participant

By signing below, I ……..……. agree to take part in a research study entitled Hypothyroidism after radiotherapy for patients with head and neck cancer at Pietersburg Hospital, Limpopo Province, South Africa.

I declare that:

I have read or had this information read to me and it is explained in a language with which I am fluent and comfortable.

I have had a chance to ask questions and all my questions have been adequately answered.

I understand that taking part in this study is voluntary and I have not been pressurised to take part.

I may choose to leave the study at any time and will not be penalised or prejudiced in any way.

I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (place) .....…..... on (date) ……...…….. 2018

Signature of participant_____

Signature of witness_____

Declaration by investigator

I Dr T. Manavalan declare that:

I explained the information in this document to ……...

I encouraged him/her to ask questions and took adequate time to answer them.

I am satisfied that he/she adequately understands all aspects of the research, as discussed above

I did not use an interpreter. (If an interpreter is used then the interpreter must sign the declaration below.

Signed at (place) .....…..…… on (date) ……...…….. 2018

Signature of investigator_____

Signature of witness_____

Declaration by interpreter

I (name) ……..…… declare that:

I assisted the investigator (name) ……. to explain the information in this document to (name of participant) ……..…… using the language medium of Sepedi/Xitsonga/Tshivenda.

We encouraged him/her to ask questions and took adequate time to answer them.

I conveyed a factually correct version of what was related to me.

I am satisfied that the participant fully understands the content of this informed consent document and has had all his/her question satisfactorily answered.

Signed at (place) .....…..... on (date) ……...……...

Signature of interpreter_____

Signature of witness_____

ANNEXURE D: 1st Turfloop Research Ethics Committee Clearance Certificate

University of Limpopo
Department of Research Administration and Development
Private Bag X1106, Sovenga, 0727, South Africa
Tel: (015) 268 4029, Fax: (015) 268 2306, Email:Abdul.Maluleke@ul.ac.za

TURFLOOP RESEARCH ETHICS COMMITTEE CLEARANCE CERTIFICATE

MEETING: 02 November 2017

PROJECT NUMBER: TREC/415/2017: PG

PROJECT:

Title: Post radiation therapy hypothyroidism in patients with head and neck cancer at Pietersburg Hospital, Limpopo Province, South Africa
Researcher: TJD Manavalan
Supervisor: Dr FO Ooko
Co-Supervisor: N/A
School: School of Medicine
Degree: Masters of Medicine in Radiation Oncology

PROF TAB MASHEGO
CHAIRPERSON: TURFLOOP RESEARCH ETHICS COMMITTEE

The Turfloop Research Ethics Committee (TREC) is registered with the National Health Research Ethics Council, Registration Number: **REC-0310111-031**

Note:
i) **Should any departure be contemplated from the research procedure as approved, the researcher(s) must re-submit the protocol to the committee.**
ii) **The budget for the research will be considered separately from the protocol.**
PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.

Finding solutions for Africa

ANNEXURE E: 2nd Turfloop Research Ethics Committee Clearance Certificate

University of Limpopo
Department of Research Administration and Development
Private Bag X1106, Sovenga, 0727, South Africa
Tel: (015) 268 3935, Fax: (015) 268 2306, Email: anastasia.ngobe@ul.ac.za

TURFLOOP RESEARCH ETHICS COMMITTEE

ETHICS CLEARANCE CERTIFICATE

MEETING: **17 August 2021**

PROJECT NUMBER: **TREC/415/2017: PG-Renewed**

PROJECT:

Title:	Post radiation therapy hypothyroidism in patients with head and neck cancer at Pietersburg Hospital, Limpopo Province, South Africa.
Researcher:	TJD Manavalan
Supervisor:	Dr FO Ooko
Co-supervisor :	N/A
School:	Medicine
Degree:	Masters of Medicine in Radiation Oncology

PROF P MASOKO
CHAIRPERSON: TURFLOOP RESEARCH ETHICS COMMITTEE

The Turfloop Research Ethics Committee (TREC) is registered with the National Health Research Ethics Council, Registration Number: **REC-0310111-031**

Note:

i) **This Ethics Clearance Certificate will be valid for one (1) year, as from the abovementioned date. Application for annual renewal (or annual review) need to be received by TREC one month before lapse of this period.**

ii) **Should any departure be contemplated from the research procedure as approved, the researcher(s) must re-submit the protocol to the committee, together with the Application for Amendment form.**

iii) **PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.**

Finding solutions for Africa

ANNEXURE F: Permission to conduct the study in Limpopo Province

LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

Department of Health

Ref : LP_2021-08-021
Enquires : Ms PF Mahlokwane
Tel : 015-293 6028
Email : Phoebe.Mahlokwane@dhsd.limpopo.gov.za

Tijo Manavalan

PERMISSION TO CONDUCT RESEARCH IN DEPARTMENTAL FACILITIES

Your Study Topic as indicated below;

Post radiation therapy hypothyroidism in head and neck cancer patients at Pietersburg hospital, Limpopo Province, South Africa

1. Permission to conduct research study as per your research proposal is hereby Granted.
2. Kindly note the following:
    a. Present this letter of permission to the institution supervisor/s a week before the study is conducted.
    b. In the course of your study, there should be no action that disrupts the routine services, or incur any cost on the Department.
    c. After completion of study, it is mandatory that the findings should be submitted to the Department to serve as a resource.
    d. The researcher should be prepared to assist in the interpretation and implementation of the study recommendation where possible.
    e. The approval is only valid for a 1-year period.
    f. If the proposal has been amended, a new approval should be sought from the Department of Health
    g. Kindly note that, the Department can withdraw the approval at any time.

    Your cooperation will be highly appreciated

_____ 13/09/2021_____

pp **Head of Department** **Date**

ANNEXURE G: Pietersburg Mankweng Hospital Research Ethics Committee Certificate

LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

DEPARTMENT OF HEALTH
PIETERSBURG/MANKWENG RESEARCH ETHICS COMMITTEE (PMREC)

ENQUIRIES: DR MA POOPEDI **DATE: 21 JULY 2021**

MANAGER: CLINICAL RESEARCH

ananiaspoopedi@gmail.com

REFERENCE	:	**PMREC 21 JULY UL 2021/C**
DATE	:	**21 JULY 2021**
RESEARCHER	:	**DR T MANAVALAN**
		(PRINCIPAL INVESTIGATOR)
RESEARCH	:	**POST-GRADUATE RESEARCH**
DEPARTMENT	:	**RADIATION ONCOLOGY**

Protocol Title : Post radiation therapy hypothyroidism in patients with head and neck cancer at Pietersburg hospital, Limpopo province.

CANDIDATE : **DR T MANAVALAN**

APPROVAL STATUS : **APPROVED**

SIGNED:

PROF TAB MASHEGO

Prof TAB Mashego, PhD
Chairperson: Pietersburg/Mankweng Complex Research Ethics Committee
School of Medicine
University of Limpopo
REC 300408-006

ANNEXURE H: Editor's Note

N J Nel
PO Box 365,
BENDOR PARK
0713

Tel: xxxxxxxx

CERTIFICATE

This serves to certify that I have language edited the Dissertation of

Dr Tijo Jospaul Davis Manavalan

Student number: **XXXXXXXXX**

entitled:

"POST RADIATION THERAPY HYPOTHRYOIDISM IN HEAD AND NECK CANCER PATIENTS IN PIETERSBURG HOSPITAL, LIMPOPO PROVINCE, SOUTH AFRICA"

N J Nel

Lecturer of English, Department Applied Languages
Tshwane University of Technology
(Retired)

1 Oct. 2021