

Radioactive Iodine in the Management of Thyrotoxicosis

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Master of Medicine
In
Radiotherapy and Oncology**

By

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DECLARATION

I, Dr Neil Yeshwant Narsai declare that

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LIST OF ABBREVIATIONS

ATD	Anti-Thyroid Drug
DNA	Deoxyribonucleic Acid
FT3	Free Tri-Iodothyronine
FT4	Free Thyroxine
GD	Graves Disease
Gy	Gray (unit of absorbed radiation dose)
^{131}I	Radioactive Iodine
IALCH	Inkosi Albert Luthuli Central Hospital
MBq	Mega-Bequerel (unit of radioactivity) – 10^6 disintegrations per second
mCi	MilliCurie (unit of radioactivity) – 3.7×10^7 disintegrations per second
MNG	Multi-Nodular Goitre
RAI	Radioactive Iodine
TA	Toxic Adenoma
TFT	Thyroid Function Test
TND	Toxic Nodular Disease
TPO	Thyroid Peroxidase
TSH	Thyroid Stimulating Hormone (Thyrotropin)

ABSTRACT OF THE DISSERTATION

Objective : An audit of the use and outcomes of Radioactive Iodine (RAI) therapy in the definitive management of thyrotoxicosis at Inkosi Albert Luthuli Central Hospital (IALCH), KwaZulu-Natal, South Africa.

Methods : The clinical records of all new patients with thyrotoxicosis, referred in a 4 year period between 01/01/2003 and 31/12/2006, were analysed. Response to RAI was monitored using biochemical parameters (namely, Thyroid Stimulating Hormone and Free T4 levels). Rates of euthyroidism (cure), hypothyroidism and hyperthyroidism (treatment failure) were correlated to dose of RAI. Patients were followed-up for at least 2 years or until the onset of hypothyroidism. The follow-up period was until 31/12/2007.

Results : One hundred and fourteen patients (37.7%), of a cohort of 302 new thyrotoxic patients treated with RAI, met the inclusion criteria. Ninety-six patients (84.2%) had Graves Disease (GD) whilst 18 had Toxic Nodular Disease (TND).

At 2 year follow-up, 91 patients (79.8%) were hypothyroid, 10 (8.8%) were euthyroid and 13 (11.4%) were hyperthyroid. The average dose of RAI to achieve euthyroidism was 10mCi and hypothyroidism, 9.7mCi. The average time to achieve euthyroidism was 5.9 months and 10.1 months to become hypothyroid. Thirty-one patients (27.2%) remained persistently hyperthyroid after one dose of RAI.

Patients with GD (88.5%) were more likely to become hypothyroid ($p < 0.001$) whilst 38.9% of TND patients remained hyperthyroid ($p = .001$). Baseline TFT values were significant in terms of outcomes correlated with the prescribed RAI dose i.e Low Dose ($<8\text{mCi}$) vs. Intermediate Dose ($8\text{-}9\text{mCi}$) vs. High Dose ($>9\text{mCi}$)(TSH $p = 0.05$; FT4 $p = 0.003$; FT3 $p = 0.001$).

Conclusion : The majority of patients became hypothyroid over time, in keeping with reported data. In the public health sector, where early access to RAI (in terms of waiting times for appointments for RAI) and follow-up are major problems, early cure is essential to minimize the morbidity of thyrotoxicosis and this may be achieved with an initial high dose of RAI.

CHAPTER 1 : INTRODUCTION

Radioactive Iodine (RAI) has been used in the management of thyroid disorders for over 70 years.¹ In an age of rapid emergence of radiopharmaceuticals, RAI represents the prototype therapy in radiation medicine, with its list of clinical indications continually expanding.²

In the South African public healthcare system where patients with thyrotoxicosis commonly present late and experience delays in diagnosis and referral, the role of RAI in the early management of thyrotoxicosis is crucial.³ Rapid, effective intervention is often required to render patients euthyroid. Due to a lack of Nuclear Medicine physicians in KwaZulu-Natal, RAI is prescribed by Clinical Oncologists working in the Department of Radiotherapy and Oncology at Inkosi Albert Luthuli Central Hospital (IALCH) and Addington Hospital. Long waiting lists for first visit appointments at the Oncology clinic result in thyrotoxic patients being commenced on Anti-Thyroid Drugs (ATDs) to control moderate-to-severe thyrotoxicosis before definitive therapy with RAI.

Thyroidectomy and ATDs remain viable options for the management of selected patients with thyrotoxicosis, but these modalities have been superseded by RAI in the last two decades, particularly in the United States of America.⁴

Hypothyroidism is the commonest side-effect of RAI therapy.^{1,5,6,7,8,9} This usual consequence of RAI treatment is considered by endocrinologists, nuclear medicine

physicians and radiation oncologists to be an acceptable end-point of RAI therapy.^{8,10,11} The development of hypothyroidism is easily managed with thyroid hormone supplementation and the available data suggests that this therapy confers a benefit in terms of reducing long-term morbidity and mortality associated with thyrotoxicosis.^{12,13}

RAI therapy is also reported to be associated with a modest increase in risk of secondary malignancy. Large epidemiological studies of RAI in the management of thyrotoxicosis have identified a cancer-associated standardized mortality ratio (SMR) of 1.02, that is not considered clinically significant (95% CI 0.98-1.07) for doses of RAI ranging between 7-10mCi^{14,15,16,17}; the clinical benefit of RAI outweighs the risk of carcinogenicity.¹

The need for life-long monitoring of thyroid function and follow-up to evaluate for the development of secondary malignancy is well-recognised.¹ Follow-up at primary care level is lacking and, unlike in the developed world, the responsibility of follow-up is borne by regional and tertiary facilities.

CHAPTER 2 : THYROTOXICOSIS

Indications for Radioactive Iodine

Radioactive Iodine has been used in a number of benign thyroid diseases, often with different dose regimens and with variable treatment intents.^{9,13,18,19,20} Amongst the common indications for the use of RAI are : Graves' disease (GD), toxic multinodular goitre (MNG), toxic adenoma (TA) and non-toxic goitre.

Graves' Disease

Graves' disease (GD) is an autoimmune disease characterized by thyroid hyperfunction that is initiated by stimulatory auto-antibodies to the thyrotropin (TSH) receptor protein which is located on the thyrocyte cell membrane. The thyroid stimulating antibodies bond to the TSH receptor, activating adenylate cyclase, resulting in increased thyroid hormone production, increase in thyroid gland size and increased vascularity.²¹

GD is a condition that is typically characterized by episodes of remission and relapse. GD is more common in young adults and in females and accounts for between 60-80% of all cases of thyrotoxicosis. It may be familial and may also be associated with other autoimmune diseases. Up to 50% of patients with GD may also have an infiltrative ophthalmopathy.²¹

The diagnosis of GD is made by a combination of clinical, biochemical and scintigraphic findings. Clinically, patients present with a diffuse goiter with or without a bruit, characteristic eye signs (including proptosis and ophthalmoplegia), signs and

symptoms of hyperthyroidism or a concomitant autoimmune disease. Biochemically, serum TSH is low and serum FT4 and FT3 are elevated. Thyroid antibodies are usually elevated. Radionuclide uptake scans show a diffuse, uniformly increased uptake of the radioisotope.¹

Treatment options in GD include : antithyroid drugs, thyroidectomy and RAI – all of which have their own benefits and risks.^{4,21,22} The use of steroids in GD is only advocated in the setting of severe ophthalmopathy.⁷

Toxic Multinodular Goitre

Toxic multinodular goitre (MNG) is characterized by mixed population of hyper-functioning and hypo-functioning nodules embedded in normal thyroid tissue. It is more common in adults over the age of 50 and in females. The proposed aetiology includes goitrogens, hereditary factors, environmental factors and hormonal factors. Toxic MNG is up to ten times more common in iodine-deficient areas. The nodules in a toxic MNG are said to be autonomous i.e. independent of control exerted by TSH. Advances in molecular biology have suggested that nodular proliferation is caused by over-expression of the RAS proto-oncogene, resulting in TSH receptor activation and up-regulation of cyclic adenosine monophosphate (cAMP) signaling.^{23,24,25}

The diagnosis of toxic MNG is made on clinical, biochemical and radiological studies. Patients often present with a nodular goitre and signs and symptoms of hyperthyroidism. These are usually older patients with long-standing disease and

they typically also have co-morbid thyrocardiac manifestations. Biochemically, TSH is suppressed and FT4 and FT3 are elevated. Thyroid antibodies are usually negative. Ultrasound scan of the thyroid demonstrates a nodular thyroid whilst radionuclide thyroid scan is characterized by heterogenous uptake with foci of increased irregular uptake corresponding to the autonomous nodules.^{1,23}

Toxic Adenoma

Toxic adenoma (TA) refers to a solitary autonomous hyper-functioning nodule in the thyroid parenchyma. Thyroid tissue is composed of a small fraction of cells with an inherent ability to proliferate in the absence of a recognizable stimulus. This replicative potential results in local hyperplasia and eventually, the formation of an adenomatous nodule. Less than 25% of all adenomas will secrete thyroid hormones. Inactive nodules have a finite life-span and usually undergo degeneration and apoptosis. Toxic adenoma is a condition with a slow evolution, but tends to occur in slightly younger patients than toxic MNG.^{1,25,26}

Patients usually present with symptoms of thyrotoxicosis, with a palpable nodule in the thyroid gland. The thyroid function test reflects this toxicosis and thyroid scintigraphy is very accurate in delineating a nodule which intensely concentrates the radionuclide.^{1,23}

Non-Toxic Goitre

Non-toxic goitre refers to thyroid enlargement in the absence of hyperthyroidism. This may arise sporadically or may occur in endemic areas of iodine deficiency.

Incidence increases with age and it is more common in females. These goitres increase in size progressively, but at a variable rate. They eventually come to medical attention due to cosmetic or obstructive symptoms. Whilst surgery remains the mainstay in the treatment of this condition, RAI has been used to effect a reduction in the size of the thyroid gland, with favourable results.²⁵

CHAPTER 3 : RADIOACTIVE IODINE

Radioactive Iodine : A Historical Perspective

The discovery of RAI as a diagnostic and therapeutic tool in the management of benign and malignant thyroid disorders is widely considered to have heralded the birth of Nuclear Medicine as a speciality. This was preceded by pioneering work in the fields of thyroid physiology and radiochemistry. The integration of these two fields in the 1940s was the ultimate precursor to RAI which is used worldwide in the clinical setting today.^{27,28}

In 1895, Baumann described the presence of iodine in the thyroid gland. Subsequently, Marine discovered that the thyroid cleared iodine from the blood. Kendall isolated a crystal form of iodine, now known as thyroxine.²⁵

These physiological discoveries were paralleled in the field of radiochemistry, by the work of Henri Becquerel who, in 1896 in collaboration with Marie Curie discovered radioactivity. During the same generation, Ernest Rutherford proposed the concepts of half-life and the decay constant. Alpha (α), beta (β) and gamma (γ) radiation were characterised. The Curies experimented extensively with radioactivity as a medical adjunct. In 1913, Abbe used Radium to treat hyperthyroidism.²⁵

Many new radioisotopes were discovered during this period. Additionally, scientists started to manufacture artificial radioisotopes. By the 1930s, research into the applications of radionuclides was relentless, both in the clinical and laboratory

setting. As with earlier work in the field of radioactivity, much of the research in radionuclide use was centred around the management of malignancies.²⁷

Radioactive iodine was discovered prior to the Second World War. Early experiments involved laboratory animal thyroid physiology. The war however, resulted in a slow-down in this research, as the attentions of the radio-physicists were channelled into the production of the Atomic Bomb. The subsequent carnage in Hiroshima and Nagasaki has ultimately proved to be both beneficial and detrimental to the development and use of radionuclides in the clinical setting. On the one hand, nuclear radiation became shackled with negative connotations whilst on the other, survivors of the bombings provided vital information on the effects of radiation in long-term follow-up studies.²⁵

In 1942, radioactive iodine was first reported to be used in the treatment of thyroid cancer. Patients who were faced with a dismal prognosis were being offered the chance of a cure. The dramatic results obtained resulted in a fast-tracking of radioisotopes into clinical use via the Atomic Energy Act of 1946. In 1951, the Food and Drug Administration (FDA) in the United States of America approved radioactive iodine for the treatment of benign thyroid diseases.²⁹

Radioactive iodine has been used to elucidate the finer details of thyroid physiology, from the uptake mechanism of iodine, to the synthesis of thyroid hormone and serum transport of these hormones.²⁷

The γ -emitting properties of radioactive iodine were harnessed by Anger and colleagues who developed the gamma camera that facilitated imaging of the thyroid, thereby providing valuable information on a wide range of thyroid disorders. This was later superseded by the discovery and use of Technetium-99 (^{99m}Tc).²⁸

Indeed, ^{131}I is considered to be the fore-runner of numerous radiopharmaceuticals, including 18-Fluorodeoxyglucose (^{18}FDG) which is widely used in Positron Emission Tomography (PET) scanning, 90-Yttrium labelled ibritumomab tiuxetan which is used in follicular B-cell lymphoma and 89-Strontium, used in the palliation of bone metastases. ^{131}I has found other uses in clinical oncology, namely in the management of neuroendocrine tumours like pheochromocytomas, using ^{131}I mIBG and ^{131}I -tositumomab which is used in the treatment of relapsed refractory follicular B-cell lymphoma.²⁷

The Radiobiology of Radioactive Iodine

The biological basis of RAI therapy lies fundamentally in the ability of the thyroid gland to concentrate iodine. Negligible amounts of iodine are taken up in the salivary glands, stomach and bladder.³⁰

Radioactivity is defined as the number of nuclear disintegrations per second. The unit of radioactivity used at our centre, both in the departments of Nuclear Medicine and Radiation Oncology, is the milliCurie (mCi) which is equal to 3.7×10^7

disintegrations per second. The other unit of radioactivity used at other centres is the Mega Becquerel (MBq) which equates to 10^6 disintegrations per second. By mathematical deduction, $1\text{mCi} = 37\text{MBq}$.²⁸

The "Absorbed Dose" refers to the amount of energy transferred by ionizing radiation to a given mass of tissue. It is expressed in Joules per kilogram (J/kg) and the SI unit is the gray (Gy).²⁸

The "Effective Dose" seeks to standardize or weight the radiation exposure since different types of tissue react differently to different types of radiation. The SI unit for effective dose is the milliSievert (mSv) and this has important implications in the field of Radiation Protection.²⁸

Radioactive Iodine (^{131}I) decays with a physical half-life of 8.1 days. The biological half-life of ^{131}I is highly variable and is determined by the clearance of ^{131}I from the thyroid. The mean effective half-life is a combination of the biological and physical half-lives and approximates 6 days. Approximately 80% of ^{131}I is cleared renally.

The decay of ^{131}I is by Beta (β^-) particle emission to ^{131}Xe .^{9,29}

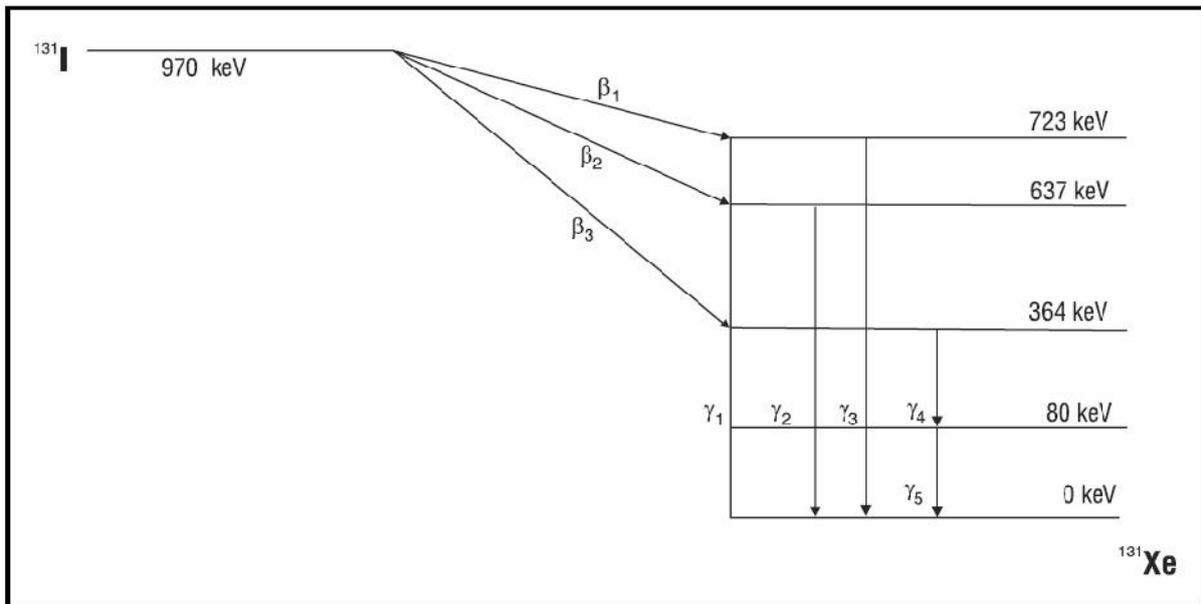


Figure 1 : Decay Schema of ^{131}I (from Meller J. Sahlmann CO. Becker W. Radioiodine treatment of functional autonomy)⁹

β_3 emission is the principal β^- particle and carries an average energy of 0.61 MeV

The majority of ^{131}I (90%) decays to the 364 keV (γ_1), 7% to the 637 keV (γ_2) and 2% to the 723 keV (γ_3) excited level of ^{131}Xe . All nuclei in the 723 keV and 637 keV decay by γ -emission ($\gamma_2 + \gamma_3$) directly to the ground state. Of the 364 keV group, 7% of nuclei decay via the 80 keV level (γ_4).²⁸

Oral ^{131}I is absorbed via the gastrointestinal tract vasculature and preferentially taken up by the thyroid gland.²⁷

^{131}I is actively taken up by the thyroid follicular cell via the sodium-iodine symporter on the basolateral membrane on the thyrocyte. Iodide is transported through the intracellular space towards the apical cell surface, to the follicular lumen. This is facilitated by the chloride-iodine transport protein, pendrin. Iodide undergoes

oxidation to Iodine by thyroid peroxidase at the luminal surface of the apical membrane of the epithelium.²⁵

¹³¹I is a medium range β^- emitter with a range in thyroid tissue of 0.4-0.8mm. The β^- particles produce more than 90% of the dose to the thyroid tissue whilst the γ emission is utilised in imaging modalities of the thyroid.²⁷

In normal thyroid tissue, the follicular cells range in diameter from 0.05-0.50mm. Hyperfunctioning thyrocytes have considerably smaller diameters (ranging from 0.075-0.15). Homogenous distribution on thyroid scans predicts a homogenous dose distribution through the thyroid gland. The more vascular the gland, the better the distribution of the dose.²⁷

The biological effects of ¹³¹I and radiation in general, result from chemical changes at the molecular level.⁷ These changes may be brought about directly or indirectly. Direct action is produced by high linear energy transfer (LET) radiation. β^- particles deposit their energy within macro-molecules, usually DNA, causing ionization and excitation of the molecule, ultimately altering its conformation and function.²⁸

Indirect action occurs when radiation interacts with other molecules or atoms to produce free radicals ($H\cdot$; $OH\cdot$) which in-turn interact with DNA. Free radicals have an outer-shell unpaired electron that is highly reactive. The simplest free radical is $H\cdot$ which is active in an aqueous environment, a characteristic of thyroid follicular cells.

DNA integrity is vital for cell survival. Free radicals interact with both the base and sugar components of the DNA molecule. The OH[·] free radical reacts with bases by the addition of a double bond and with the sugars by hydrogen ion abstraction.

These reactions induce DNA damage by :

- Breakage of hydrogen bonds resulting in structural damage.
- Loss of or change in nitrogenous bases which may be lethal or result in a mutation.
- DNA single-strand breaks which may be repairable.
- DNA double-strand breaks which are invariably lethal.
- Cross-linking between 2 DNA molecules.

The net result of these interactions is *cell death or functional impairment*.^{27,30}

Histological findings in cells which have been exposed to ¹³¹I include epithelial swelling and necrosis, oedema and leucocyte infiltration. Within two weeks of RAI administration, there is follicular breakdown and disruption with leakage of extracellular colloid. Fibrosis starts about three to four weeks later.^{29,30}

Radiation thyroiditis is an entity that may occur one to three days after RAI therapy. It is characterised by oedema, tenderness, hyperaemia, hyperthermia and dysphagia. In this time interval, there may be a paradoxical rise in thyroid hormone level. This flare phenomenon is usually due to the release of stored thyroid hormone from damaged follicles. In its most severe form, this surge in thyroid hormone may cause thyroid storm. The incidence in one large clinical study was 0.34%.¹⁵ Large

goitres have the potential to cause local compressive symptoms on the trachea and oesophagus, post-RAI. Retrosternal goitres may additionally give rise to superior vena cava syndrome due to the acute inflammatory response. The use of RAI in these settings is advocated, only in the presence of strict monitoring.²⁴ The use of lithium to potentiate the activity of RAI has largely fallen out of favour.³¹

Late changes due to RAI have been assessed by analyzing histopathological specimens ranging from four months to twelve years post-RAI. These specimens show marked fibrosis, follicular disruption and irregular hypoplastic follicles, with associated eosinophilia and telangiectasia.³² The radiation fibrosis tends to be progressive over the years. Regeneration of follicles tends to be sporadic, focal and irregular. The neoplastic potential of this RAI damage has not proven to be increased, when compared to the general population.^{2,29,30}

Cell survival curves are important tools employed in radiobiology to illustrate dose-response relationships.³⁰

Due to the delivered dose being dependent on mean effective half-life, the cellular effect of ¹³¹I is prolonged, with estimates suggesting that 95% of the total dose is delivered within the first four weeks post-¹³¹I administration.^{28,30}

Dose Strategies for Radioactive Iodine

There are 3 approaches to selecting an optimal dose of RAI in patients with Thyrotoxicosis.^{1,24,33,34} These include the fixed administered radioactivity method, the prescribed radioactivity concentration method and the prescribed absorbed dose method.

The Fixed Administered Radioactivity Method

This is also known as the Fixed Dose Method. A fixed radioactivity of 185-370MBq (5-10mCi) is given to all patients irrespective of clinical, radiological or biochemical variables.⁵⁶ The doses mentioned have been validated in multiple clinical trials over the last 20 years.^{6,10,17,36,37} A modification of the fixed dose method is the one that is used at IALCH, where the dose selected for the individual patient is at the discretion of the prescribing healthcare practitioner.³⁶

The Prescribed Radioactivity Concentration Method

In this model, a fixed radioactivity per gram of thyroid tissue is chosen. This is usually in the range of 55-110 μ Ci/g in order to deliver a dose of 50-100Gy to the thyroid. The administered radioactivity is calculated according to the gland size and the percentage uptake of RAI at 24 hours in a tracer test. This method has been proven in a few trials and is the preferred strategy at many centres. The following formula is then used to determine the dose³⁸ :

$$\text{Activity (mCi)} = (\text{mCi/g} \times \text{estimated gland mass (g)} \times 100) / (\text{24hour \% uptake})$$

The Prescribed Absorbed Dose Method

The administered activity is calculated according to the following equation :

$$\text{Activity (mCi)} = (\text{Prescribed absorbed dose} \times \text{gland mass} \times 6.67) / (T_{1/2(\text{eff})} \times 24\text{hour \% uptake})$$

Where the effective half-life of RAI, $T_{1/2(\text{eff})}$ is given by the equation :

$$1/T_{1/2(\text{eff})} = 1/T_{1/2(\text{phys})} + 1/T_{1/2(\text{bio})}$$

A scintillation counter is required to determine the percentage uptake of RAI tracer. The absolute uptake is difficult to measure and is considered to be a function of the exponential decay of RAI – this in itself is not mono-exponential. As a result, a relative uptake value is calculated over a 24 hour period.^{16,20} Additionally, medical physicists have derived many complex radiobiological equations to try to make the procedure more accurate. This process has proven to be very time-consuming, inconvenient to the patient and costly, with minimal, if any clinical benefit.^{34,39} An additional flaw in the calculated dose methodology is the estimation of thyroid gland mass. Radio-isotope scans are inaccurate and there is significant clinician-clinician variability in estimating gland mass, even amongst endocrinologists who have been using this method.^{39,40}

Factors that Influence Outcome in RAI Therapy

Dose

A wide spectrum of clinical trials have demonstrated that higher doses of RAI are invariably associated with a higher cure rate (euthyroidism), whilst also being associated with a higher incidence of hypothyroidism.^{5,6,15,41,42,43,44}

Radiosensitivity

The RAI dosage models described above attempt to tailor dose according to individual patient requirements. Attempts to predict radiosensitivity, by measuring uptake of RAI into thyrocytes, have not proven to be consistent or reproducible. These strategies may over-simplify the actual biological behavior of the thyrotoxic gland, but they remain popular throughout the world.^{20,34,38}

Antithyroid Drugs (ATDs)

ATDs are often used in the initial management of GD. Many patients will achieve euthyroidism on these drugs and can be maintained on them for a few years. Over time, ATDs decelerate the uptake of iodine by the thyrocyte. This potentially reduces the therapeutic effect of RAI when administered later in the clinical course of the disease. As such, it is widely believed that ATDs may exert a radio-protective effect.¹¹ Studies have demonstrated that failure to stop ATDs within three days of RAI administration, reduced the uptake and subsequent radiobiological effect of RAI.^{45,46,47,48}

Thyroid Size

Patients with large goiters have been shown to have poorer response rates to RAI therapy. The enlarged thyroid gland is often differentially radiosensitive and whilst estimating size and weight of the gland may be valuable predictors theoretically, these models may only be applicable in Graves' Disease, where iodine uptake is homogenous.^{6,49}

CHAPTER 4 : PATIENTS AND METHODS

AIM

The aim of the study was to undertake an audit of the use of Radioactive Iodine (RAI) in the definitive management of thyrotoxicosis at Inkosi Albert Luthuli Central Hospital (IALCH), the quaternary referral centre in KwaZulu-Natal, South Africa.

OBJECTIVES

To determine:

- the incidence of clinical and biochemical cure (euthyroidism)
- the incidence of hypothyroidism post RAI
- the incidence of clinical & biochemical failure post RAI – defined as persistent hyperthyroidism
- the optimal dose of RAI

METHOD

This is a *retrospective observational study* of adult patients (> 15 years old) with thyrotoxicosis, referred for the first time to the Clinical Oncology Department at Inkosi Albert Luthuli Central Hospital (IALCH) by the Endocrinology department in a four year period between 01/01/2004 and 31/12/2007.

The study was approved by the research ethics committee and the postgraduate education committee of the University of KwaZulu-Natal (BE116/08). IALCH is the quaternary referral centre in the province of KwaZulu-Natal.

Most patients were commenced on carbimazole on diagnosis of thyrotoxicosis whilst awaiting definitive RAI therapy. The dose of RAI prescribed and administered was clinician-dependent and within the recommended minimum and maximum doses. Patients were followed-up at the Endocrinology clinic at IALCH. Response to RAI was monitored using biochemical parameters (namely, serum Thyroid Stimulating Hormone and Free T4 levels). Incidence of euthyroidism (cure), hypothyroidism and hyperthyroidism (treatment failure) were correlated with dose of RAI. Patients were followed-up for at least two years or until the onset of hypothyroidism. The follow-up period was until 31/12/2007.

Data was collected and collated using Date Capture sheets (Appendix A)

Data collected included:

Demographic data:	Age, gender
Clinical data:	Aetiology, co-morbid cardiac disease
Biochemical data:	Thyroid function tests
Immunological data:	Thyroid antibodies (where available)
Radiological data:	Radio-isotope scan (where available)
Dosimetric data:	Dose of radioactive iodine, cumulative dose

DEFINITION OF TREATMENT OUTCOMES

Euthyroidism[§]: normal level of serum thyroid hormone.

Hypothyroidism[§]: clinical condition of a deficit of thyroid hormone in the blood, defined by serum TSH > 4.20mU/L, FT4 < 12.20pmol/L or FT3 < 3.50pmol/L [¥]

Hyperthyroidism[§]: clinical condition of increased thyroid hormone in the blood, defined by serum TSH < 0.10mU/L, FT4 > 22.70pmol/L or FT3 > 6.50pmol/L [¥]

([§]Outcome assessed in the absence of medical therapy i.e. carbimazole or thyroxine;

[¥]Reference laboratory values at IALCH)

STATISTICAL ANALYSIS

Statistical analysis was undertaken using SPSS Version 15.0. (SPSS Inc, Chicago, Ill, USA). Mean \pm SD was used for continuous variables. A p-value of < 0.05 was considered to be statistically significant and 95% confidence intervals were also reported where appropriate. For multiple (intergroup) comparisons, Bonferroni's test, oneway analysis of variance (ANOVA), inverse chi-square testing and Levene's tests were used.

CHAPTER 5 : RESULTS

5.1 Total Study Group Baseline Characteristics

A total of 302 patients with thyrotoxicosis were treated with RAI during the defined study period (01 January 2004 - 31 December 2007). These constituted referrals from the Endocrinology Clinic at IALCH, Addington Hospital, RK Khan Thyroid Clinic and external sources.

Of the 302 patients treated, only 114 (37.7%) patients met the inclusion criteria for this retrospective study and they form the "total study group".

The inclusion criteria were :

- New referral to the Oncology Clinic
- Age > 15
- Follow-up for at least two years after the first dose of RAI or until the onset of hypothyroidism

The remaining 188 patients were either lost to follow-up or continued their follow-up at their referral hospital.

Table 1 shows the baseline characteristics of the study group (n = 114). The majority of the patients were female, accounting for 97 (85.1%), whilst there were 17 (14.9%) males. Ninety-six (84.2%) patients had GD, 15 (13.2%) had toxic MNG and there were three (2.6%) patients with TA. Cardiac disease was documented in

25 patients (21.9%). Eighty-eight (77.2%) patients had pretreatment with the ATD, carbimazole.

Table 1 : Baseline characteristics of the study group (n=114).

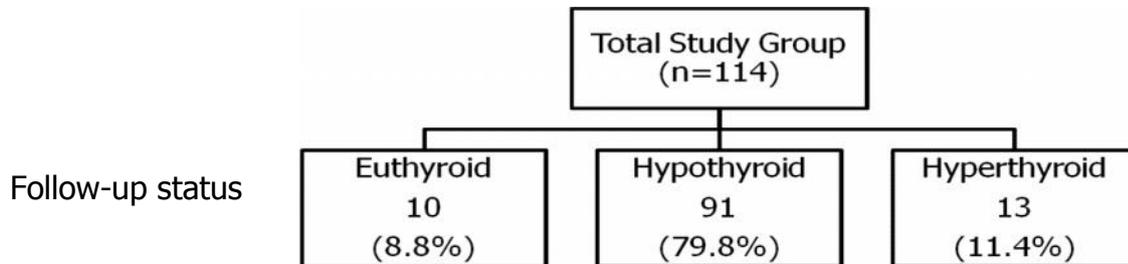
Characteristic	n (%)
Gender	
Male	17 (14.9%)
Female	97 (85.1%)
Mean age (years)	46.1 ± 13.8
Diagnosis	
Graves disease (GD)	96 (84.2%)
Toxic multinodular goitre (MNG)	15 (13.2%)
Toxic adenoma (TA)	3 (2.6%)
Cardiac disease	
Yes	25 (21.9%)
No	89 (78.1%)
Pre-RAI carbimazole	
Yes	88 (77.2%)
No	26 (22.8%)

5.2 Follow-up Status

At two year follow-up, ten patients (8.8%) were euthyroid, 91 (79.8%) were hypothyroid and 13 (11.4%) hyperthyroid. Amongst the 17 male patients, at minimum of two years of follow-up, 16 were hypothyroid and one patient remained hyperthyroid. Amongst the females, 75 patients (77.3%) were hypothyroid, ten (10.3%) were euthyroid and 12 (12.4%) were hyperthyroid. (Figure 2)

Figure 2 : Two year follow-up status in the total study group (n = 114)

Baseline



Thirty-one (27.2%) patients remained persistently hyperthyroid after the first dose of RAI and required repeated doses of RAI; these were deemed to represent treatment failures.

5.3 RAI dose requirements

The initial dose prescribing patterns at the centre range from 5 – 12mCi (Table 2) with a mean initial dose of 8.5 ± 1.4 mCi . Thirty-one (27.2%) patients remained hyperthyroid after the initial dose of RAI and required a second dose of RAI, six patients required a third dose, one patient a fourth dose and one patient received five doses of RAI.

Table 2 : Initial RAI dose requirements in the study group (n=114)

Dose (mCi)	Frequency (n)	Percent (%)
5	2	1.8
6	1	0.9
7	21	18.4
7.5	1	0.9
8	49	43.0
10	39	34.2
12	1	0.9

The cumulative dose of RAI prescribed ranged from 5 - 46mCi, with a mean dose of 11.0 ± 5.5 mCi.

5.4 Outcomes

Table 3 summarizes treatment outcomes at two year follow-up, based on the aetiology of thyrotoxicosis

Table 3 : Treatment outcomes at two year follow-up, based on aetiology (n = 114)

Aetiology	Euthyroid	Hypothyroid	Hyperthyroid
Graves' disease (n = 96)	7 (7.3%)	83 (86.5%)	6 (6.2%)
Multinodular goiter (n = 15)	2 (13.3%)	8 (53.3%)	5 (33.3%)
Toxic adenoma (n = 3)	1 (33.3%)	0	2 (66.7%)

Of the 96 patients with GD, 17 were male and 79 female. The mean age of the male patients was 40.6 years (17-66), whilst the mean age for female patients was 45.6 years (18-79). The mean dose of RAI prescribed was 10.8mCi (5-46mCi). At two year follow-up, seven patients (7.3%) were euthyroid, 83 (86.5%) were hypothyroid and six (6.2%) patients remained hyperthyroid.

There were 15 patients with MNGs, all of whom were female. Mean age was 54.4 years (36-76). The mean administered dose of RAI was 13.3mCi (5-24mCi). At a minimum of two years of follow-up, two patients (13.3%) were euthyroid, 8 (53.3%) were hypothyroid and five patients (33.3%) remained hyperthyroid.

In the three patients that had TAs, the dose of RAI administered, ranged from 8-15mCi, with a mean dose of 10.3mCi. One patient was euthyroid and two patients remained hyperthyroid at two year follow-up.

Time and dose requirements for euthyroidism

Analysis of the time and dose required to achieve euthyroidism was done, based on aetiology of the thyrotoxicosis. Only one patient with TA achieved euthyroidism – she received 8mCi and was euthyroid after eight months. Ten patients with MNG achieved a euthyroid state, eight of whom subsequently developed hypothyroidism at two year follow-up. They received a mean dose of 12mCi (5-24mCi) and the mean time to euthyroidism was 12.5 months (3-27 months). Ninety patients with GD became euthyroid after RAI, with 83 eventually becoming hypothyroid, in the absence of medical therapy. Of the 17 males treated, the mean dose of RAI was

9.6mCi (7-20mCi) and the mean time to euthyroidism was 5.2 months (1-28 months). Seventy-three female patients with GD became euthyroid during follow-up. The mean dose of RAI was 9.8mCi (5-20mCi) and the mean time to euthyroidism was 5.8 months. Six patients with GD were still hyperthyroid after the minimum two year follow-up. The mean dose of RAI administered, was 23.7mCi (10-46mCi). Five patients with toxic MNG remained hyperthyroid despite repeated doses of RAI. The mean cumulative dose prescribed was 17mCi (14-21mCi). For the purposes of data analysis, TA & MNG patients were grouped together as "Toxic Nodular Disease" (TND). The mean time to euthyroidism for TND was 10.0 months. In those patients with TND who became hypothyroid, the mean time was 9.1 months.

5.4.1 Analysis by dose of RAI

Table 4 depicts the stratification of patient characteristics and outcomes according to the prescribed dose i.e. into Low dose ($\leq 7.5\text{mCi}$), Intermediate dose (8-9mCi) and High dose ($\geq 10\text{mCi}$).

There were no significant differences in the dose of RAI prescribed, based on age, gender, the presence or absence of cardiac disease or pre-treatment with ATDs. (Appendix B, Tables I – IV)

In contrast, there were significant differences in the doses prescribed, based on the baseline TSH, FT4 and FT3. Subjects who were prescribed a high dose of RAI, had significantly higher baseline TSH, FT4 and FT3, when compared to those who were prescribed a low dose of RAI. They also had a significantly higher FT4 and FT3 when

compared to those patients who were given an intermediate dose of RAI. No difference in baseline TFTs was observed between the groups who received a low dose or intermediate dose of RAI. (Tables 4 - 8)

The dose of RAI that was prescribed had no significant effect on the incidence of euthyroidism, hypothyroidism or hyperthyroidism, nor did it have an effect on the time taken to attain euthyroidism or hypothyroidism in those patients who were cured. (Appendix B, Tables V – XI)

For the subjects who received a low dose of RAI, none achieved euthyroidism. Eighty-eight percent (88%) of patients who received a low dose of RAI became hypothyroid and 12% remained hyperthyroid.

For those patients given an intermediate dose of RAI, the rates of euthyroidism, hypothyroidism and hyperthyroidism were 14.3%, 77.5% and 8.2% respectively.

Amongst those patients given a high dose of RAI, 7.5% were euthyroid, 77.5% became hypothyroid and 15% remained hyperthyroid.

Table 4 also shows the mean cumulative doses of RAI eventually prescribed, for patients receiving an initial low, intermediate and high dose of RAI. As expected the difference in total dose between the three dose groups was significant. Details of intergroup analysis by ANOVA and Bonferroni tests are shown in Tables 9 and 10.

Table 4 : Stratification by prescribed dose of RAI in the total study group (n = 114)

	RAI Dose (mCi)				p *	95% CI
	Total	Low Dose (≤ 7.5) n=25	Intermediate Dose (8-9) n=49	High Dose (≥ 10) n=40		
Female n(%)	97 (85.1%)	22 (88%)	42 (85.7%)	33 (82.5%)	0.8	
Male n(%)	17 (14.9%)	3 (12%)	7 (14.3%)	7 (17.5%)		
Age	46.1 \pm 13.8	46.7 \pm 18.0	45.7 \pm 12.4	46.3 \pm 12.7	0.9	
Cardiac n(%)	25 (21.9%)	5 (20%)	9 (18.4%)	11 (27.5%)	0.6	
ATD n(%)	88 (77.2%)	17 (68%)	38 (77.6%)	33 (82.5%)	0.4	
Baseline TFT						
TSH (mU/L)	1.1 \pm 4.8	3.1 \pm 8.9 [§]	0.1 \pm 3.4	0.01 \pm 0.5	0.05	0.01 - 5.83
FT4 (pmol/L)	43.9 \pm 30.1	34.8 \pm 30.3 [§]	38.0 \pm 26.0 [¥]	56.9 \pm 30.9	0.003	3.91 - 39.87
FT3 (pmol/L)	16.8 \pm 13.3	12.6 \pm 11.5 [¥]	14.0 \pm 11.1 [¥]	22.8 \pm 14.9	0.001	2.22 - 17.98
Total Dose (mCi)	11.02 \pm 5.51	8.74 \pm 3.9 [¥]	10.2 \pm 4.25 [§]	13.4 \pm 6.8	0.001	0.49 - 7.93
Follow-up thyroid status (%)						
Hyperthyroid	13 (11.4%)	3 (12%)	4 (8.2%)	6 (15%)	0.6	
Euthyroid	10 (8.8%)	0	7 (14.3%)	3 (7.5%)	0.1	
Hypothyroid	91 (79.8%)	22 (88%)	38 (77.5%)	31 (77.5%)	0.5	
Time (months) to						
Euthyroid	5.9 \pm 5.7	4.8 \pm 4.8	6.2 \pm 6.2	6.2 \pm 5.6	0.6	2.26 - 5.16
Hypothyroid	9.9 \pm 8.3	9.0 \pm 7.1	9.9 \pm 8.6	10.4 \pm 8.7	0.8	4.18 - 7.06

Mean \pm SD unless otherwise stated. * p values using ANOVA or chi-square test. § vs high dose, p < 0.05 using Bonferroni's test. ¥ vs high dose, p < 0.01 using Bonferroni's test. ATD : Anti-thyroid drug.

Table 5 : Intergroup analysis based on prescribed dose of RAI - ANOVA (TFTs)

		Sum of Squares	df	Mean Square	F	Sig.
TSH	Between Groups	136.026	2	68.013	3.079	.050
	Within Groups	2451.686	111	22.087		
	Total	2587.712	113			
FT4	Between Groups	10455.532	2	5227.766	6.319	.003
	Within Groups	91830.878	111	827.305		
	Total	102286.410	113			
FT3	Between Groups	2244.643	2	1122.322	7.043	.001
	Within Groups	17688.774	111	159.358		
	Total	19933.417	113			

Table 6 : Intergroups analysis based on prescribed dose of RAI - Bonferroni Tests (TSH)

(I)first dose	(J)first dose	Mean Diff (I-J)	Std. Error	Sig.	95% CI	
					Lower Bound	Upper Bound
Low	Intermediate	2.22191	1.15510	.171	-5.589	5.0297
	High	2.71740	1.19820	.049	.0048	5.8300
Intermediate	Low	-2.22191	1.15510	.171	-5.0297	.5859
	High	.69549	1.00147	1.000	-1.7389	3.1299
High	Low	-2.71740	1.19820	.049	-5.8300	-.0048
	Intermediate	-.69549	1.00147	1.000	-3.1299	1.7389

Table 7 : Intergroup analysis based on prescribed dose of RAI - Bonferroni Tests

(FT4)

(I)first dose	(J)first dose	Mean Diff (I-J)	Std. Error	Sig.	95% CI	
					Lower Bound	Upper Bound
Low	Intermediate	-3.23156	7.06937	1.000	-20.4158	13.9527
	High	-22.04010	7.33313	.010	-39.8655	-4.2147
Intermediate	Low	3.23156	7.06937	1.000	-13.9527	20.4158
	High	-18.80854	6.12914	.008	-33.7073	-3.9098
High	Low	-22.04010	7.33313	.010	4.2147	39.8655
	Intermediate	18.80854	6.12914	.008	3.9098	33.7073

Table 8 : Intergroup analysis based on prescribed dose of RAI - Bonferroni Tests

(FT3)

(I)first dose	(J)first dose	Mean Diff (I-J)	Std. Error	Sig.	95% CI	
					Lower Bound	Upper Bound
Low	Intermediate	-1.40737	3.10267	1.000	-8.9493	6.1346
	High	-10.16155	3.21843	.006	-17.9849	-2.3382
Intermediate	Low	1.40737	3.10267	1.000	-6.1346	8.9493
	High	-8.75418	2.69001	.005	-15.2931	-2.2153
High	Low	10.16155	3.21843	.006	2.3382	17.9849
	Intermediate	8.75418	2.69001	.005	2.2153	15.2931

Table 9 : Intergroup analysis based on prescribed dose of RAI - ANOVA (Total Dose)

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	392.330	2	196.165	7.158	.001
Within Groups	3041.866	111	27.404		
Total	3434.195	113			

Table 10 : Intergroup analysis based on prescribed dose of RAI - Bonferroni Tests (Total Dose)

(I)first dose	(J)first dose	Mean Diff (I-J)	Std. Error	Sig.	95% CI	
					Lower Bound	Upper Bound
Low	Intermediate	-1.484	1.287	.753	-4.61	1.64
	High	-4.685	1.335	.002	-7.93	-1.44
Intermediate	Low	1.484	1.287	.753	-1.64	4.61
	High	-3.201	1.116	.015	-5.91	-.49
High	Low	4.685	1.335	.002	1.44	7.93
	Intermediate	3.201	1.116	.015	.49	5.91

5.4.2 Analysis by aetiology

Table 11 stratifies the patient cohort according to the aetiology of their thyrotoxicosis.

The difference in gender distribution between patients with GD and TND, was not statistically significant. (Appendix B, Table XII) Patients with TND were significantly older (54.0 ± 12.3) than those with GD (44.7 ± 13.6), $p = 0.008$. (Table 12)

Patients with GD had a higher baseline FT4 (45.92pmol/L vs 33.33pmol/L , $p = 0.04$) and FT3 (17.83pmol/L vs 11.33pmol/L , $p = 0.006$). The difference in mean TSH levels between the two groups, was not significant. (Table 13)

There was no significant difference in the mean first dose of RAI (GD vs. TND : 8.6mCi vs. 7.9mCi) nor in the total dose of RAI that was prescribed for either GD (10.7mCi) or TND (12.8mCi). (Appendix B, Table XIII)

Euthyroidism was achieved in 5.2% of patients with GD and 27.8% of those with TND ($p = 0.009$). There was a significantly higher incidence of hypothyroidism amongst patients with GD (88.5% vs 33.3%, $p < 0.001$). The incidence of hyperthyroidism was significantly higher in patients with TND (38.9%) than in those with GD (6.3%) ($p = 0.001$). (Table 14 – 16)

Patients with GD had a mean time to euthyroidism of 5.38 months and time to hypothyroidism of 9.94 months. For those with TND, the mean time to euthyroidism

was 10.00 months, whilst mean time to hypothyroidism was 9.14 months; However, there was no significant difference between the two groups. (Appendix B, Table XIV)

Table 11 : Stratification by aetiology in the total study group (n = 114)

	Total (n=114)	Graves Disease (n=96)	Toxic Nodular Disease (n=18)	p*	95% CI
Baseline					
Female n(%)	97 (85.1%)	79 (82.3%)	18 (100%)		
Male n(%)	17 (14.9%)	17 (17.7%)	0	0.1	
Age (years)	46.1 ± 13.8	44.7 ± 13.6	54.0 ± 12.3	0.008	
TSH (mU/L)	1.07 ± 4.8	1.23 ± 5.2	0.18 ± 0.7	0.4	1.4 - 3.5
FT4 (pmol/L)	43.9 ± 30.1	45.9 ± 31.3	33.3 ± 20.5	0.04 [‡]	0.8- 24.3
FT3 (pmol/L)	16.8 ± 13.3	17.8 ± 13.9	11.3 ± 7.4	0.006	2.0 - 11.0
1st Dose (mCi)		8.6 ± 1.3	7.9 ± 1.2	0.1	0.04 - 1.3
Total Dose (mCi)	11.0 ± 5.5	10.7 ± 5.4	12.8 ± 6.0	0.1	0.6 - 4.9
At follow-up					
Hyperthyroid n(%)	13 (11.4%)	6 (6.3%)	7 (38.9%)	0.001	
Euthyroid n(%)	10 (8.8%)	5 (5.2%)	5 (27.8%)	0.009	
Hypothyroid n(%)	91 (79.8%)	85 (88.5%)	6 (33.3%)	<0.001	
Time (months) to					
Euthyroid	5.9 ± 5.7	5.4 ± 5.0	10.0 ± 9.0	0.1	1.5 - 10.7
Hypothyroid	9.9 ± 8.3	9.9 ± 8.3	9.1 ± 8.5	0.8	5.7 - 7.2

Mean ± SD, except where stated. * p values using ANOVA or chi-square test. ‡ Confidence interval crosses unity, so comparison not significant

Table 12 : Independent samples test based on aetiology (Age)

	Levene's Test for Equality of Variances		t-test for Equality of Means		Sig. (2-tailed)	Mean Difference	Std Error Difference	t-test for Equality of Means	
	F	Sig.	t	df				95% CI	
								Lower	Upper
Equal Variances Assumed	.080	.778	-2.175	112	.008	-9.354	3.446	-16.181	-2.527
Equal Variances Not Assumed			-2.915	25.503	.007	-9.354	3.209	-15.956	-2.752

Table 13 : Independent samples test based on aetiology (TFTs)

		Levene's Test for Equality of Variances		t-test for Equality of Means					95% CI	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std Error Difference	Lower	Upper
TSH	Equal variances assumed	2.563	.112	.853	112	.396	1.04955	1.23062	-1.38877	3.48786
	Equal variances not assumed			1.887	108.968	.062	1.04955	.55624	-.05290	2.15199
FT4	Equal variances assumed	7.712	.006	1.641	112	.104	12.58670	7.67047	-2.61134	27.78475
	Equal variances not assumed			2.176	33.925	.037	12.58670	5.78524	.82873	24.34467
FT3	Equal variances assumed	7.647	.007	1.927	112	.057	6.49486	3.37119	-.18471	13.17443
	Equal variances not assumed			2.889	43.546	.006	6.49486	2.24829	1.96239	11.02734

Table 14 : Chi-square tests based on aetiology (Hyperthyroidism)

	Value	df	Asym. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	15.983 ^a	1	.000		
Continuity Correction ^b	12.916	1	.000		
Likelihood Ratio	11.965	1	.001		
Fisher's Exact test				.001	.001
Linear-by-Linear Association	15.843	1	.000		
N of Valid Cases	114				

a. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 2.05

b. Computed only for a 2x2 table

Table 15 : Chi-square tests based on aetiology (Euthyroidism)

	Value	df	Asym. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	9.648 ^a	1	.002		
Continuity Correction ^b	7.034	1	.008		
Likelihood Ratio	7.214	1	.007		
Fisher's Exact test				.009	.009
Linear-by-Linear Association	9.564	1	.002		
N of Valid Cases	114				

a. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 1.58

b. Computed only for a 2x2 table

Table 16 : Chi-square tests based on aetiology (Hypothyroidism)

	Value	df	Asym. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	28.687 ^a	1	.000		
Continuity Correction ^b	25.362	1	.000		
Likelihood Ratio	23.379	1	.000		
Fisher's Exact test				.000	.000
Linear-by-Linear Association	28.436	1	.000		
N of Valid Cases	114				

a. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 3.63

b. Computed only for a 2x2 table

5.4.3 Analysis of treatment outcomes

Table 17 outlines the baseline characteristics based on treatment outcome at follow-up.

Ninety-six patients had GD, whilst the remaining 18 had TND. There was a significant overall difference for treatment outcomes between the group with GD and that with TND ($p < 0.001$). Intergroup analysis (Table 17) showed that the majority of GD patients (88.5%) became hypothyroid, whilst hypothyroidism only occurred in 33.3% (6/18) of TND patients. Only 6.3% (6/96) of GD patients remained persistently hyperthyroid whilst 38.9% (7/18) of TND patients failed RAI therapy.

There were no significant predictive factors for treatment outcome amongst the variables analyzed in this cohort of patients (gender, age, cardiac status, use of ATDs, baseline TFT and dose of RAI). (Appendix B, Tables XV – XXV)

Table 17 : Baseline characteristics of study group based on disease outcomes at 2 year follow-up

	Thyroid status at follow-up				p*
	Total (n=114)	Euthyroid (n=10)	Hypothyroid (n= 91)	Hyperthyroid (n=13)	
Female n(%)	97 (85.1%)	10 (100%)	75 (82.4%)	12 (92.3%)	0.2
Male n(%)	17 (14.9%)	0	16 (17.6%)	1 (7.7%)	
Age	46.1 ± 13.8	45.6 ± 14.6	45.4 ± 13.8	51.7 ± 13.1	0.3
Graves Disease n(%)	96 (84.2%)	5 (50%)	85 (93.4%)	6 (46.2%)	0.000
Toxic Nodular Disease n(%)	18 (15.8%)	5 (50%)	6 (6.6%)	7 (53.8%)	
Cardiac n(%)	25 (21.9%)	3 (30%)	17 (18.7%)	5 (38.5%)	0.2
Carbimazole (n%)	88 (77.2%)	7 (70%)	73 (80.2%)	8 (61.5%)	0.3
TSH (mU/L)	1.1 ± 4.8	0.3 ± 0.9	1.3 ± 5.3	0.7 ± 0.2	0.6
FT4 (pmol/L)	43.9 ± 30.1	41.7 ± 26.5	43.2 ± 29.9	50.7 ± 35.3	0.7
FT3 (pmol/L)	16.8 ± 13.3	14.6 ± 12.1	16.3 ± 12.7	22.1 ± 17.5	0.3
Dose of RAI					0.3
Low n(%)	25	0	22 (24.2%)	3 (23.1%)	
Intermediate n(%)	49	7 (70%)	38 (41.7%)	4 (30.7%)	
High n(%)	40	3 (30%)	31 (34.1%)	6 (46.2%)	
Total Dose (mCi)	11.0 ± 5.5	12.4 ± 5.4	9.7 ± 3.4	19.4 ± 9.4	0.2

Mean ± SD, except where stated. * p values using ANOVA or chi-square test.

Table 18 : Chi-square Tests based on disease outcomes (Aetiology)

	Value	df	Asym. Sig. (2-sided)
Pearson Chi-Square	28.750 ^a	2	.000
Likelihood Ratio	23.413	2	.000
Linear-by-Linear Association	23.849	1	.000
N of Valid Cases	114		

a. 2 cells (33.3%) have expected count less than 5. The minimum expected count is 1.58

CHAPTER 6 : DISCUSSION

Although RAI has been in clinical use for over 70 years, there remains no consensus on the optimal dose that is required to cure patients. Whilst most clinicians consider hypothyroidism to be an acceptable, unavoidable end-point, others consider it to be a side-effect.^{6,35,43} This study was undertaken with the aim of evaluating the treatment outcomes at the local centre, in the hope of offering some guidelines for the initial and total dose of RAI to be administered.

A major issue highlighted in this study, is the poor patient follow-up. Three hundred and two (302) patients received RAI during the defined study period. Only 114 (37.7%) met the inclusion criteria, largely on the basis of not being followed-up at the treatment centre. This factor remains a challenge that is well-documented by similar studies in developing countries.^{10,31,36,50,51}

Thyroidectomy and ATDs are recognized modalities in the management of thyrotoxicosis. Topping *et al.* randomised 179 patients with GD to receive either ATDs, surgery or RAI. Medically treated patients were at highest risk of relapse. However, a high failure rate (38%) was found in the RAI arm, although there was a high patient satisfaction rate for all modalities, assessed by quality of life questionnaires.²¹ The cost and morbidity associated with surgery means that ATDs and RAI are the preferred therapeutic modalities at most centres in the world.^{1,24}

From the available literature, the prevalence of thyrotoxicosis in the general population is estimated at 2% in women and 0.2% in males,²⁹ with GD being the commonest cause of thyrotoxicosis in iodine-sufficient areas.^{1,34} In this study, GD accounted for 84.2% of all cases. The finding of a female preponderance (85.1%) is comparable with that reported in the literature. There was a larger cohort of cardiac patients (21.9%) in this study, when compared to reported rates of thyrocardiac disease that range between 2-20% (12.1% in the study by Kwok *et al*).⁴⁰ This may be accounted for by the late presentation of patients in the local public health sector.

The cure rate after the first dose of RAI (72.8%) in this study is comparable with available reports (which predominantly evaluated GD), which cite success rates of 60 – 92%.^{1,12,36} The overall GD cure rate at two year follow-up was 95.7%. Patients who failed to respond to an initial dose of RAI, were offered a repeat dose. The use of repeated doses of RAI is a validated treatment option, both in terms of safety and efficacy.^{2,52} Metso *et al*. reported that 25% of their patient cohort of 2043 patients required repeated doses of RAI, with no significant increase in morbidity.²⁹

Early hypothyroidism rates for RAI therapy in GD range from 20 - 76% and 11 - 34% for Toxic MNG.^{2,5,6,8,15,19,23,25,29} Nygaard and colleagues reported a 92% cure rate for Danish patients with MNG with a five year hypothyroidism rate of only 14%; the median dose used was 370MBq (10mCi).²³ In contrast, the outcomes of patients with TND in this study, were less impressive with a treatment failure rate of 39.9%

and a hypothyroidism rate of 33.3%. There was no significant difference between the doses of RAI that were prescribed for patients with GD and those with TND.

The finding that more than one-third of patients with GD in this study developed hypothyroidism is consistent with those documented in most studies that included a heterogenous population of thyrotoxic patients.^{5,6,8,10,17,25,29,40,49}

RAI dose is considered to be a significant contributing factor for the development of hypothyroidism.^{6,35} However, in this study there was no direct correlation between RAI dose and therapeutic outcome or on the time to achieve a cure. This is validated in other studies that made a similar observation.^{6,10,17,25,29,40,41} There are however, other confounding studies that suggest that a high dose of RAI results in significantly higher cure rates, albeit with a higher rate of hypothyroidism.^{2,5,8,16,41} Not all studies that used a higher dose of RAI, demonstrated a higher rate of hypothyroidism.^{1,25,40}

In this study, the dose of RAI prescribed was according to a modified fixed-dose method that was dependent on the attending Clinical Oncologist.^{2,5,8,16,41} The only significant factor that influenced the decision on the dose of RAI that was administered was the patient's baseline thyroid function tests. Those patients who received a high dose of RAI had a significantly higher baseline TSH, FT4 and FT3 than those who received a low dose of RAI.

From available literature, reports of cure rates with fixed dose RAI have been variable.^{10,35,42,51,54} Alexander *et al.* used a fixed dose of 8mCi of RAI and reported an

impressive cure rate of 86%.³⁵ In a weight-adjusted retrospective study by Bastan-Hagh *et al.* there was a 91.2% cure rate, with 57.7% of patients being rendered hypothyroid.¹⁰

Sankar *et al.* conducted a prospective study to assess their practice of empirical low-dose RAI, with the aim of trying to avoid hypothyroidism. Of the 174 patients evaluated at one year follow-up, 16.7% were euthyroid, 29.3% hypothyroid and 54% remained persistently hyperthyroid. Those patients who failed RAI therapy received a significantly lower dose and the authors concluded that their policy of empirical low-dose RAI needed to be changed, to increase the cure rate.⁵¹

In one of the few South African studies undertaken on doses of RAI and outcomes, Kalk *et al.* reported on 150 patients who were treated with low dose (mean 2.8mCi) and moderate dose RAI (mean 5.9mCi). At one year follow-up, there was an unacceptably high rate of persistent hyperthyroidism (39%) in patients who received low dose RAI, as opposed to 19% for the moderate dose. The conclusion was that low dose RAI is unsuitable for the management of thyrotoxicosis.⁴² This was further validated in a British study by Hoskin, which showed no benefit of using fixed low dose RAI.⁵⁴

The three different methods of determining RAI dose (fixed dose, calculated dose and absorbed dose), have been the subject of many published reports. Several studies have shown that calculated doses of RAI do not have any benefit over fixed doses, in terms of cure rate.^{25,40} Although low fixed doses are associated with low

rates of hypothyroidism, they result in low cure rates.²² A French study by Catargi and colleagues analyzed the effectiveness of individual dosimetric calculation. They established that delivered doses to the thyroid were highly variable and unpredictable and recommended that calculated RAI doses be abandoned in favour of the fixed dose method.³⁹

The fixed dose RAI method has been shown to be equivalent to the prescribed radioactivity concentration method and the prescribed absorbed dose method, in terms of treatment outcome.^{1,36,38,39} The fixed dose method is however simple, reproducible and more cost-effective and is therefore used at the local hospital and at most centres worldwide.^{1,6,25,27,29,40}

Kwok *et al.* reported results from a study in 2000 that utilized a fixed dose of RAI in 149 patients. The treatment success rate was 66%. Patients who used ATDs were at a higher risk of treatment failure. The rate of hypothyroidism at three year follow-up was 73%. The use of fixed dose RAI was much less resource-intensive, more cost-effective and more user-friendly and was recommended as a routine practice.^{40,58}

There were no significant predictors of outcome to RAI therapy identified in this study.

Numerous attempts have been made to identify predictors of outcome in the use of RAI. Allabadhia *et al.* reported that in patients with GD, those with large goitres, severe biochemical disease, men and younger patients were less likely to respond to

a single dose of RAI.⁶ Additional poor prognostic factors include high 24 hour thyroid ¹²³I uptake value and pretreatment with ATDs for more than four months.^{4,35}

Younger patients tend to have more severe hyperthyroidism at presentation.^{8,55} Yamashita *et al.* reported that younger patients were more likely to have persistent hyperthyroidism after RAI therapy and require higher doses of RAI, than older patients.⁵⁶ This factor was not analyzed in this study.

In a retrospective study from the Mayo Clinic, the authors reported that the following factors predicted higher rates of hypothyroidism : age < 40 years, pre-treatment with ATDs, higher dose of RAI and smaller estimated thyroid gland size.⁸ Although patients in this study who developed hypothyroidism were younger, this was not statistically significant.

The results of this study which showed no significant predictors of outcome to RAI, may be accounted for by the small sample size, the retrospective nature of the study or the fact that crucial variables may not have been analysed or were missing (eg. thyroid volume and RAI uptake).

Regarding the impact of pretreatment with ATDs, in this study, patients who were pre-treated with carbimazole did not display any difference in outcome compared to those who were not given carbimazole. Similar observations were reported by Andrade and colleagues, who showed that ATD use had no effect on both cure and hypothyroidism.⁵⁷ In contrast, Sabri *et al.* reported a success rate of 93% vs. 49%

($p < 0.001$) in favour of those not pre-treated with ATDs,⁴⁷ as did a Danish study which showed that the use of propylthiouracil as pre-treatment resulted in a reduced cure rate.⁴⁶ On the other hand, a Swiss study demonstrated that stopping ATDs at least three days prior to RAI therapy, did not negatively impact on cure rates.⁴⁸

Although outcomes between ethnic groups was not analyzed as part of this study, Kalk *et al.* reported definite differences in terms of presentation between white and African (black) patients with hyperthyroidism. In their study, African patients presented more frequently with more severe thyrotoxicosis, cardiac disease and infiltrative ophthalmopathy. The observed differences were postulated to be due to African patients presenting much later which was attributed to possible differences in awareness of the disease, based on education, cultural beliefs and economic factors.³

Studies conducted prior to the 1990s suggested a preference for medical therapy and surgery over RAI, due to safety concerns, especially the perceived increased risk of cancer, infertility and teratogenicity. Read *et al.* published data of a 36 year retrospective analysis that confirmed the safety and efficacy of RAI used in 116 patients younger than 20 years old at initial diagnosis.⁵⁹

Large epidemiological studies undertaken in the UK, USA and Sweden, demonstrated a small relative increase in risk of diagnosis and mortality from thyroid cancer in patients treated with RAI. Extensive follow-up of these studies seem to suggest that

the risk is related to underlying thyroid disease rather than RAI therapy.⁶⁰ This study has too short a follow-up duration to assess for carcinogenicity.

CHAPTER 7 : CONCLUSION

RAI has an established role in the management of thyrotoxicosis, as it is clinically safe and cost-effective, when compared with other treatment modalities. It is generally considered to be the gold-standard, but the ideal dosing strategy remains an area of great controversy.

Although the three available strategies have benefits and limitations, none has been shown to be superior in predicting the efficacy and outcomes of RAI therapy. The strategy followed at IALCH, is the fixed-dose method (although in reality, the dose varied according to individual discretion) and the data presented (in terms of cure and treatment failure rates) compares favourably with reported data from other centres worldwide.

This study shows that regardless of dose, the majority of patients eventually become hypothyroid. Historical and contemporary studies advocate abandoning the use of low doses of RAI due to unacceptably high rates of treatment failure. The reported treatment failure rate in this study was 27.2% which although comparable with other studies must be appreciated in the context of poor patient attendance at follow-up.

The lack of significant identifiable predictive factors, the almost inevitable outcome of hypothyroidism and the relative safety of RAI, presents a strong argument in favour of using a high dose of RAI (10mCi) at the outset, in order to maximize the

chance of a cure, particularly in the setting of high rates of poor follow-up in the local public healthcare system.

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APPENDIX A :

KZ _____

DATA COLLECTION SHEET

PATIENT DEMOGRAPHICS

AGE _____

GENDER

MALE	
FEMALE	

CAUSE OF TOXICOSIS

Graves Disease	
Toxic Multinodular Goitre	
Toxic Adenoma	
Unclassified	

CARDIAC DISEASE

Y
N

THYROID FUNCTION TESTS

DATE										
TSH										
FT4										
FT3										

THYROID ANTIBODIES _____

RADIOISOTOPE SCAN _____

RADIOACTIVE IODINE (RAI)

DOSE ; DATE 1. _____ mCi; _____
 2. _____ mCi; _____
 3. _____ mCi; _____
 4. _____ mCi; _____

CUMULATIVE DOSE _____ mCi

FOLLOW-UP AFTER RAI

	0-6m	6-12m	12-18m	18-24m	24-30m	30-36m
DATE						
Hyperthyroid						
Euthyroid						
Hypothyroid						
No Follow-up						
Repeat RAI						

TIME TO REPEAT RAI DOSE _____ Mnths _____
 _____ Mnths _____
 _____ Mnths _____

TIME TO EUTHYROIDISM _____ Mnths _____

TIME TO HYPOTHYROIDISM _____ Mnths _____

APPENDIX B

1. Analysis by dose-stratification

1.1 Baseline Characteristics (Chapter 5, Page 27)

Table I : Chi-squared tests based on prescribed dose of RAI (Gender)

	Value	df	Asym. Sig. (2-sided)
Pearson Chi-Square	.393 ^a	2	.821
Likelihood Ratio	.394	2	.821
N of Valid Cases	114		

a. 1 cells (16.7%) have expected count less than 5. The minimum expected count is 3.73

Table II : ANOVA based on prescribed dose of RAI (Age)

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	15.790	2	7.895	.041	.960
Within Groups	21466.491	111	193.392		
Total	21482.281	113			

Table III : Chi-square tests based on prescribed dose of RAI (Cardiac)

	Value	df	Asym. Sig. (2-sided)
Pearson Chi-Square	1.143 ^a	2	.565
Likelihood Ratio	1.121	2	.571
Linear-by-Linear Association	.675	1	.411
N of Valid Cases	114		

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 5.48

Table IV : Chi-square tests based on prescribed dose of RAI (Carbimazole)

	Value	df	Asym. Sig. (2-sided)
Pearson Chi-Square	1.844 ^a	2	.398
Likelihood Ratio	1.791	2	.408
Linear-by-Linear Association	1.746	1	.186
N of Valid Cases	114		

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 5.48

1.2 Outcomes (Chapter 5, Page 28)

Table V : Chi-square tests based on prescribed dose of RAI (Euthyroidism)

	Value	df	Asym. Sig. (2-sided)
Pearson Chi-Square	4.346 ^a	2	.114
Likelihood Ratio	6.266	2	.044
Linear-by-Linear Association	.557	1	.455
N of Valid Cases	114		

a. 3 cells (50.0%) have expected count less than 5. The minimum expected count is 2.19

Table VI : Chi-squared tests based on prescribed dose of RAI (Hypothyroidism)

	Value	df	Asym. Sig. (2-sided)
Pearson Chi-Square	1.329 ^a	2	.515
Likelihood Ratio	1.457	2	.483
Linear-by-Linear Association	.864	1	.353
N of Valid Cases	114		

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 5.04

Table VII : Chi-square tests based on prescribed dose of RAI (Hyperthyroidism)

	Value	df	Asym. Sig. (2-sided)
Pearson Chi-Square	1.030 ^a	2	.597
Likelihood Ratio	1.039	2	.595
Linear-by-Linear Association	.259	1	.611
N of Valid Cases	114		

a. 2 cells (33.3%) have expected count less than 5. The minimum expected count is 2.85

1.3 Time to euthyroidism and hypothyroidism

Table VIII : ANOV A based on prescribed dose of RAI (Euthyroidism)

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	31.783	2	15.891	.487	.616
Within Groups	3194.792	98	32.600		
Total	3226.574	100			

Table IX : ANOV A based on prescribed dose of RAI (Hypothyroidism)

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	27.2055	2	13.527	.196	.823
Within Groups	6226.644	90	69.185		
Total	6253.699	92			

Table X : Intergroup analysis Bonferroni tests (Time to euthyroidism)

(I)first dose	(J)first dose	Mean Diff (I-J)	Std. Error	Sig.	95% CI	
					Lower Bound	Upper Bound
Low	Intermediate	-1.360	1.485	1.000	-4.98	2.26
	High	-1.358	1.562	1.000	-5.16	2.45
Intermediate	Low	1.360	1.485	1.000	-2.26	4.98
	High	.001	1.297	1.000	-3.16	3.16
High	Low	1.358	1.562	1.000	-2.45	5.16
	Intermediate	-.001	1.297	1.000	-3.16	3.16

Table XI : Intergroup analysis Bonferroni tests (Time to hypothyroidism)

(I)first dose	(J)first dose	Mean Diff (I-J)	Std. Error	Sig.	95% CI	
					Lower Bound	Upper Bound
Low	Intermediate	-.923	2.218	1.000	-6.33	4.49
	High	-1.438	2.304	1.000	-7.06	4.18
Intermediate	Low	.923	2.218	1.000	-4.49	6.33
	High	-.514	1.984	1.000	-5.35	4.33
High	Low	1.438	2.304	1.000	-4.18	7.06
	Intermediate	.514	1.984	1.000	-4.33	5.35

2. Analysis by aetiology

2.1 Baseline characteristics (Chapter 5, Page 33)

Table XII : Chi-Square tests based on aetiology (Gender)

	Value	df	Asym. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	3.746 ^a	1	.053		
Continuity Correction ^b	2.480	1	.115		
Likelihood Ratio	6.377	1	.12		
Fisher's Exact test				.070	.042
N of Valid Cases	114				

a. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 2.68

b. Computed only for a 2x2 table

Table XIII : Independent Samples Test based on aetiology (Dose of RAI)

		Levene's Test for Equality of Variances		t-test for Equality of Means					95% CI	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std Error Difference	Lower	Upper
1 st Dose	Equal variances assumed	5.910	.017	1.855	112	.066	.6128	.3304	-.0419	1.2676
	Equal variances not assumed			1.947	24.921	.063	.6128	.3148	-.0356	1.2613
Total Dose	Equal variances assumed	2.879	.093	-1.528	112	.129	-2.151	1.408	-4.940	.638
	Equal variances not assumed			-1.421	22.466	.169	-2.151	1.514	-5.286	.984

2.2 Time to euthyroidism and hypothyroidism (Chapter 5, Page 33)

Table XIV : Independent Samples Test based on aetiology (Time to euthyroidism and hypothyroidism)

		Levene's Test for Equality of Variances		t-test for Equality of Means					95% CI	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std Error Difference	Lower	Upper
Time to Euthyroid	Equal variances assumed	11.776	.001	-2.621	99	.010	-4.622	1.763	-8.121	-1.123
	Equal variances not assumed			-1.676	10.766	.122	-4.622	2.757	-10.707	1.463
Time to Hypothyroid	Equal variances assumed	.054	.817	.245	91	.807	.799	3.257	-5.671	7.269
	Equal variances not assumed			.239	6.954	.818	.799	3.339	-7.107	8.705

3. Analysis by disease outcomes

3.1 Baseline characteristics (Chapter 5, Page 40)

Table XV : Outcomes based on gender

		Euthyroid	Hyperthyroid	Hypothyroid	Total
Gender	F	10 (10.3%)	12 (12.4%)	75 (77.3%)	97 (100%)
	M	0	1 (5.9%)	16 (94.1%)	17 (100%)
Total		10 (8.8%)	13 (11.4%)	91 (79.8%)	114 (100%)

Table XVI : Chi-square tests based on outcomes (Gender)

	Value	df	Asym. Sig. (2-sided)
Pearson Chi-Square	2.798 ^a	2	.247
Likelihood Ratio	4.349	2	.114
N of Valid Cases	114		

a. 2 cells (33.3%) have expected count less than 5. The minimum expected count is 1.49

Table XVII : ANOVA based on outcomes (Age)

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	455.573	2	227.787	1.202	.304
Within Groups	21026.708	111	189.430		
Total	21482.281	113			

Table XVIII : Cardiac and Non-cardiac patient outcomes

		Euthyroid	Hyperthyroid	Hypothyroid	Total
Cardiac	No	7 (7.9%)	8 (9.0%)	74 (83.1%)	89 (100%)
	Yes	3 (12.0%)	5 (20.0%)	17 (68.0%)	25 (100%)
Total		10 (8.8%)	13 (11.4%)	91 (79.8%)	114 (100%)

Table XIX : Chi-square tests based on outcomes (Cardiac)

	Value	df	Asym. Sig. (2-sided)
Pearson Chi-Square	3.017 ^a	2	.221
Likelihood Ratio	2.746	2	.253
Linear-by-Linear Association	1.887	1	.170
N of Valid Cases	114		

a. 2 cells (33.3%) have expected count less than 5. The minimum expected count is 2.19

Table XX : Carbimazole effect on Outcome

		Euthyroid	Hyperthyroid	Hypothyroid	Total
Carbimazole	No	3 (11.5%)	5 (19.2%)	18 (69.2%)	26 (100%)
	Yes	7 (8.0%)	8 (9.1%)	73 (83%)	88 (100%)
Total		10 (8.8%)	13 (11.4%)	91 (79.8%)	114 (100%)

Table XXI : Chi-square tests based on outcomes Carbimazole

	Value	df	Asym. Sig. (2-sided)
Pearson Chi-Square	2.577 ^a	2	.276
Likelihood Ratio	2.364	2	.307
Linear-by-Linear Association	1.564	1	.211
N of Valid Cases	114		

a. 2 cells (33.3%) have expected count less than 5. The minimum expected count is 2.28

Table XXII : ANOVA based on outcomes (TFTs)

		Sum of Squares	df	Mean Square	F	Sig.
TSH	Between Groups	23.136	2	11.568	.501	.607
	Within Groups	2564.576	111	23.104		
	Total	2587.712	113			
FT4	Between Groups	693.508	2	346.754	.379	.686
	Within Groups	101592.902	111	915.251		
	Total	102286.410	113			
FT3	Between Groups	436.245	2	218.123	1.242	.293
	Within Groups	19497.172	111	175.650		
	Total	19933.417	113			

Table XXIII : Initial dose of RAI and Outcome

		Euthyroid	Hyperthyroid	Hypothyroid	Total
Dose	Low	0	3 (12%)	22 (88%)	25 (100%)
	Intermediate	7 (14.3%)	4 (8.2%)	38 (77.6%)	49 (100%)
	High	3 (7.5%)	6 (15%)	31 (77.5%)	40 (100%)
Total		10 (8.8%)	13 (11.4%)	91 (79.8%)	114 (100%)

Table XXIV : Chi-square tests based on outcomes (Dose)

	Value	df	Asym. Sig. (2-sided)
Pearson Chi-Square	5.146 ^a	4	.273
Likelihood Ratio	7.071	4	.132
Linear-by-Linear Association	.895	1	.344
N of Valid Cases	114		

a. 2 cells (33.3%) have expected count less than 5. The minimum expected count is 2.19

Table XXV : Intergroup analysis Bonferroni tests based on outcomes (Total Dose)

(I)outcome	(J)outcome	Mean Diff (I-J)	Std. Error	Sig.	95% CI	
					Lower Bound	Upper Bound
Euthyroid	Hyperthyroid	-6.946	1.936	.001	-11.65	-2.24
	Hypothyroid	2.719	1.533	.237	-1.01	6.45
Hyperthyroid	Euthyroid	6.946	1.936	.001	2.24	11.65
	Hypothyroid	9.665	1.365	.000	6.35	12.98
Hypothyroid	Euthyroid	-2.719	1.533	.237	-6.45	1.01
	Hyperthyroid	-9.665	1.365	.000	-12.98	-6.35