EFFICACY OF SINGLE FIXED DOSE OF RADIOIODINE (I-131) THERAPY IN PATIENTS WITH HYPERTHYROIDISM AT GROOTE SCHUUR HOSPITAL

By

Student: Ahmed Rufai Isah (ISHAHM001)

SUBMITTED TO THE UNIVERISTY OF CAPE TOWN

In partial fulfilment of the requirements for the degree of Master of Medicine (MMed)

in Nuclear Medicine

Faculty of Health Sciences

UNIVERSITY OF CAPE TOWN

Date of submission: 09 OCTOBER 2019

Supervisor: Dr. Tessa Kotze

Nuclear Medicine Division, Department of Radiation Medicine,

University of Cape Town

UNIVERSITY OF CAPE TOWN

IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

Table of Contents

DECLARATION

I, Ahmed Rufai ISAH, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: Signed by candidate

Date: 09 October 2019

2.1 ABSTRACT

Aim:

The aims of this audit were:

To determine the proportion of hyperthyroid patients receiving I-131 therapy in whom treatment with a single fixed dose was successful, as defined by the achievement of euthyroidism or hypothyroidism 6-months after the therapy;

To identify patients in whom treatment was not successful and a second dose needed;

And, if possible, to establish the factors associated with treatment failure.

Methods:

A single observer reviewed the records of all patients who received I-131 therapy for hyperthyroidism between 23rd April 2010 and 23rd November 2017 in conjunction with their pre and post treatment thyroid function tests. Results of their thyroid ultrasound were retrieved and documented. The images of their Tc-99m sodium pertechnetate thyroid scans were also retrieved and reprocessed.

Results:

The records of 409 patients treated between April 2010 and November 2017 were retrieved. 223 (63%) patients were referred by the endocrine clinic at Groote Schuur hospital (GSH. Of the 409 patients, 56 (14%) patients that were excluded because their post therapy records were not available for analysis.

Majority of our patients were females 310 (88%). Patients between the ages of 15 and 45 years are more likely to present with Grave's disease while those aged more than 45 years presented with toxic multinodular gland (p=0.000). Patients that presented between the ages of 15 and 45 years are more likely to have moderately increased pretreatment FT4 (12-51 mmol/L) (p=0.002). We administered a radioiodine therapy dose of 456.6±54.8 MBq (Mean ± SD) to these 409 patients. Among the 353 patients, with complete records, 314(89%) achieved cure at some stage after receiving one

dose of RAI; 239(76%) achieving cure ≤ 6 months of therapy and 75(24%) patients after 6 months.

In our audit the patients who failed to achieve cure following the first RAI therapy appeared to be younger (median(interquartile range) age 39(16), p= 0.03), have severe hyperthyroidism as demonstrated by higher pre-treatment FT4 (median(interquartile range) 27 pmol/L(30.6), p= 0.05) and high pertechnetate uptake (median(interquartile range) uptake 9.9%(14), p= 0.002) on thyroid scintigraphy.

CONCLUSION

Our audit showed RAI therapy was found to be successful in 68% of patients at 6 month and 89% at a year. A second therapy with radioactive iodine would be indicated in 32% of patients, as these patients have not achieved cure at 6 months. Patients presenting with severe thyrotoxicity are likely to require more than one RAI therapy. Due to major deficiencies in referral, record keeping and follow up, other factors responsible for treatment were not be able to be evaluated.

Based on these findings, suggested areas for further research are: should patients with severe hyperthyroidism be considered for pretreatment with antithyroid medication prior to RAI; would a one year follow up after radioiodine therapy be considered before second RAI.

Now that the deficiencies in our current practice have been identified and suggestions put forward to address these deficiencies, a follow up audit would be needed.

Key words: Hyperthyroidism, I-131 (Radioiodine) therapy, Effectiveness.

ACKNOWLEDGEMENT

All praises be to the Almighty Allah. By His grace I have come this far.

My appreciation and gratitude go to Professor Mike D. Mann and Dr Tessa Kotze for not only supervising this work but for their patience, unflinching support and inspiration through this journey. I equally say thank you to my teachers Drs Anita Brink, Rachelle Steyn and Naima Tag.

I am humbled and grateful to the management of Usmanu Danfodiyo University Teaching Hospital for the sponsorship. My heart felt gratitude goes to Dr Yaqub Ahmed (UDUTH, Sokoto), Dr Jawa (National Hospital, Abuja), Dr Ibrahim Abdulqadir (UDUTH, Sokoto), Dr Yaw Ampem and Dr Sofiullah Abubakar for their moral support and advice. I thank all the staff of Nuclear Medicine Department at Groote Schuur Hospital and Red Cross Hospital for their support.

To my wife, Dr Zainab and my lovely children, Fatima, Maryam, Laurat and Aisha, thank you.

LIST OF TABLES

LIST OF ABBREVIATIONS

ATDs	Anti thyroid drugs
ATA	American thyroid association
FT3	Triiodothyronine
FT4	Free tetraiodothyronine
GD	Grave's disease
GSH	Groote Schuur Hospital
I-123	Iodine 123
I-131	Iodine 131
RAI	Radioiodine
TA	Toxic adenoma
TBII	TSH binding inhibitory immunoglobulin
TMG	Toxic multinodular gland
TRab	Thyroid receptor antibody
TSH	Thyroid stimulating hormone
RAIU	Radioiodine uptake
PTU	Prophylthiouracil

1.0 RESEARCH PROTOCOL

This research protocol was submitted to and approved by the Faculty of Health Sciences, University of Cape Town before the commencement of the study.

Research topic – Efficacy of single fixed dose of radioiodine (I-131) therapy in patients with hyperthyroidism at Nuclear Medicine Department of Groote Schuur Hospital**.**

1.1 Background

Since 2011, Nuclear Medicine Department of Groote Schuur Hospital (GSH) has been conducting radioiodine therapy (RAI) for patients referred with hyperthyroidism, from Endocrine Unit of the hospital and other sites.

The Department has used the single fixed dose method of RAI administration in the management of hyperthyroidism, so the objective of this research project is to retrospectively review the therapy and assess its effectiveness.

1.2 Literature Review

Introduction

Since 2011, Nuclear Medicine Department of Groote Schuur Hospital (GSH) has been conducting radioiodine therapy (RAI) for patients referred with hyperthyroidism from Endocrine Unit of the hospital and other sites.

The objective of this research project is to retrospectively review the therapy and assess its effectiveness.

Objective of Literature Review

The Department has used the single fixed dose method of RAI administration in the management of hyperthyroidism, so this literature review focuses on the impacts of this approach on the outcome of the treatment and predictors of its failure.

Types of Studies

- Studies on the use of RAI in hyperthyroidism

Inclusion criteria

- Studies in which the outcome of a single fixed dose of radioiodine in hyperthyroidism was evaluated,
- Studies that compare the effectiveness of single dose and calculated method of determining dose were also included in the review.

Exclusion criteria

- Use of radioiodine in the treatment of cancer,

Literature search strategy

An Internet search of PubMed was undertaken. The first key phrase searched was "the use of single dose of RAI in treatment of hyperthyroidism" on the 29 August 2017. Out of the fifteen articles retrieved only ten were considered to meet the criteria and included in the review. The five that were excluded were: one full text article in Spanish, three studies that did not use RAI and addressing only a second dose.

Another phrase used was "incidence of hypothyroidism following radioiodine treatment". Of the twenty seven articles retrieved twenty three were excluded. Seven used long term follow up not applicable to this review of our practice, the full text of two articles was not accessible, three studies used the calculated method for deciding the I-131 dose, four articles did not use I-131, two studies focused on cancer therapy, one paper dealt with hyperthyroidism in children, three papers were on hypothyroidism.

Of the 28-studies and their references comparison of fixed and calculated dose of RAI in the management of hyperthyroidism was evaluated in the literature review.

Literature

Definitions

Hyperthyroidism is a clinical condition associated with high synthesis and secretion of thyroid hormone(s) by the thyroid gland. Thyrotoxicosis which is often confused with the former is a clinical state that is the result of high thyroid hormone action in tissues due to inappropriately high blood levels of thyroid hormones (1).

Symptoms and Signs of hyperthyroidism

Effects of hyperthyroidism are wide as it influences virtually all tissues and organ system; the cardiovascular system effects are one of the most deleterious(2, 3). Symptoms of overt thyrotoxicosis include heat intolerance, palpitations, anxiety, fatigue, weight loss and irregular menstruation in females(4). On examination there may be tremor, tachycardia, lid lag, and warm moist skin(2).

Diagnosis of Hyperthyroidism

Diagnosis of hyperthyroidism is made with low serum TSH level. Hyperthyroidism is generally considered as overt or subclinical, depending on the biochemical severity. Overt hyperthyroidism is diagnosed in patients with low serum level of thyroid stimulating hormone (TSH) and elevated serum triiodothyronine (T3) and/or free thyroxine (free T4) levels, while subclinical hyperthyroidism is defined as low level serum TSH with normal levels of T3 and free T4.

In order to differentiate the causes of hyperthyroidism, several investigations are available: measurement of thyroid receptor antibodies (TRab), determination of radioactive iodine uptake (RAIU), ultrasonography and I-123 or Tc-99m pertechnetate thyroid scan (1).

Types of Hyperthyroidism

Hyperthyroidism may be due to wide variety of causes among which thyroiditis, Grave's disease (GD) and toxic nodular goiter are the most common(3).

Of the many benign disease conditions that cause hyperthyroidism, only 3 are treated with radioiodine (RAI) therapy:

- Grave's disease (GD): an autoimmune disease with homogeneous increased uptake on RAI or Tc-99m pertechnetate scans.
- Toxic multinodular goiter: has heterogeneous increased uptake by the thyroid gland with or without hot nodules.
- Toxic adenoma presents as hot nodule with suppression of the uptake in the remaining thyroid gland.

Scintigraphy distinguishes these conditions from those with high serum levels of thyroid hormones and near- absent uptake in pertechnetate scan;

- Thyroiditis
- Factitious hyperthyroidism
- Struma ovarii

Treatment

According to the American Thyroid Association (ATA) guideline on the management of hyperthyroidism, all patients diagnosed with symptomatic thyrotoxicosis should be placed on β−blockade, especially elderly patients, patients with a resting heart rate of >90beats/min and patients with coexistent cardiovascular disease(1).

Three forms of treatment of the thyroid diseases associated with hyperthyroidism are available: surgery is done to patients with large goiter (≥80g) and obstructive symptoms, mostly toxic multinodular goiters(2). Kang et al(5) in 2002 reported that 96% of patients with toxic multinodular goiter had their hyperthyroidism resolved one month after thyroidectomy. Anti thyroid drugs (ATD's) is the second option; they are very effective in controlling symptoms of thyrotoxicosis. However Jia Liu et al (6)

reported in March 2017 that ATD's are associated with a high recurrence rate of up to 59% in Grave's disease patients treated with ATD's only. The third option is RAI.

Radioiodine

Iodine-131 (I-131) has been successfully used in treatment of thyrotoxicosis for more than 70 years and is now recommended as a first line treatment in some forms of thyrotoxicosis (1). Its history dates back to 1936 when Saul Hertz asked Karl Compton during a lecture presentation by the latter at Harvard Medical School, if radioactive iodine could be produced. This question triggered a series of work that led to the production of I-131, the radionuclide that is used today. I-131 was first used in a human to treat hyperthyroidism on October 12, 1941 by Hamilton and Beck(7).

I-131 emits β-particles as well as γ-rays and has a half-life of approximately 8 days. This isotope is very suitable in a therapeutic setting because its effect on the thyrocytes is primarily the result of the β-particle radiation, which has a path length of 1–2 mm. The γ-rays are important in imaging and in radiation protection(8). Currently, I-131 is available as sodium iodide in gelatine capsules and as solutions for oral application or intravenous injection. The thyroid follicular cells take up iodine. Retention of iodine in the cells depends on the metabolic activity of the cells. Approximately 30% of Iodine gets trapped by the thyroid gland and 70% directly excreted in the urine(8). After oral administration of I-131 capsule, the maximum blood level is reached approximately 3 hours later. Thyroid is the critical organ for iodine. Radioiodine is 90% excreted via urine (50% is excreted by 24 hours) and the remaining 10% via sweat and faeces(9).

Cayir et al(10) in their recent systemic review concluded that I-131 is safe and cost effective alternative to surgery and medical therapy while Chao et al(11) in 2015 reported that recurrence is less likely in patients that receive I-131 when compared with patients that receive ATD's.

The adverse effects that have been associated with the use of I-131 are either due to a transient exacerbation of hyperthyroid symptoms from radiation thyroiditis or extra thyroidal such as worsening of thyroid orbitopathy, sialadenitis, immunogenic effects, teratogenicity and carcinogenicity (8, 12).

Radioiodine therapy is contraindicated in pregnancy, lactation, patients with a thyroid nodule suspicious of thyroid cancer and patients that are unable to comply with radiation safety guidelines (1).

Radioiodine Administration

The 2016 ATA Guidelines recommend the following patient preparation prior to administration of I-131 therapy:

- Medical therapy of any comorbid disease should be optimized before I-131 therapy.
- β-adrenergic blockade medication and anti thyroid drugs (ATD) should be considered even in asymptomatic patients if they are at increased risk for complications due to worsening of hyperthyroidism (i.e., elderly patients and patients with comorbidities). The advantage of pretreatment with ATD's is that they deplete thyroid hormone stores and reduce the likely-hood of post radioiodine treatment associated transient worsening of hyperthyroidism. However, they are known to be radio protective and it has been reported that ATD's lower the uptake of I-131 by the thyroid gland and reduce its effective half-life, consequently reducing the effectiveness of the I-131 therapy(13-16). This can be compensated by discontinuation of carbimazole for 2 days or prophylthiouracil (PTU) for 2-3 weeks before giving dose of I-131(17-20).
- Patients who were on ATDs before being prepared for the therapeutic dose of I-131 and those at increased risk of worsening hyperthyroidism should resume ATDs 3 to 7 days after I-131 therapy.

Radioiodine Dose

Over the last 30 to 40 years, the aim of RAI therapy has shifted from making the

patients euthyroid to completely ablating the thyroid gland (1). The reason for this was to shorten the time during which the patient is managed for the disease process and prevent recurrence. This must be considered when interpreting papers, particularly those on the effectiveness of RAI therapy. At Groote Schuur Hospital we use the single administration of 370 MBq with the aim to render the patient hypothyroid. In South Africa we may only administer a maximum dose of 370 MBq on an outpatient basis(21), as this is the dose most likely to result in radiation measurement of 25USv/hr at 1 meter.

Low dose (<370MBq) of I-131 is associated with prolonged hyperthyroid state with its attendant morbidity and increased risks of cardiovascular complications(22) while a high dose (≥ 370 MBq) renders patients hypothyroid more quickly(23-25). Nordyke et al in their study to find an adequate fixed dose of I-131 for thyrotoxicosis in 605 patients reported that the optimal fixed dose for cure was 370MBq(26). Both Royal College of Physicians(27)and ATA (1) in their guidelines recommend dose of 370 MBq.

Another method of estimating the dose is through calculating the activity to be administered. Many formulae have been used but the most common are the Marinelli and modified Marinelli formulae. These formulae all have measured Iodine kinetics in the thyroid gland with RAIU. Other parameters used are estimated weight of the gland and target radiation dose to the gland.

$$\frac{\text{Weight} \times \text{MBq (desired)}}{\text{Uptake}}$$

Weight is estimated by palpation and is defined as x-times normal.

The desired dose used is based on the diagnosis i.e 5.5MBq for Grave's disease and 7.5MBq for toxic multinodular goiter.

Uptake of iodine by the thyroid is measured 24h after an I-131 tracer dose using a collimated scintillation probe and compared with a neck phantom. These are corrected for background radiation.

$$\text{Uptake is calculated} = \frac{\text{Patient's count} - \text{background}}{\text{Phantom counts- background}} \times 100$$

There is no difference in the therapeutic outcome associated with this method and it increases complexity in the patients' management and cost while fixed dose is more effective(10, 28-31).

1.3.2 Effectiveness of single fixed dose

During follow up, the effectiveness of radioiodine therapy is assessed with the history, clinical examination and serum levels of TSH and FT4. It has been recommended that interpretation of serum TSH within the first two months of receiving I-131 be done with caution as TSH may remain suppressed for a long period after hyperthyroidism resolves(1). Follow up of patients starts at six weeks post therapy in our center and treatment success is defined as the attainment of euthyroidism or hypothyroidism within a period of three to six months post therapy. This is in-line with the ATA recommendations and is well documented in India(32), the Middle east(33) and Europe(34, 35).

The reports on the effectiveness of a single fixed dose I-131 and the factors that affect outcome differ. Many reports describe equal success rates with the lower dose (<370 MBq) and a higher dose (≥370 MBq) of I-131(36-43). Allahabadia et al(44) and Schneider et al(45) in retrospective studies reported that there were statistically significant different cure rates between patients who received single doses of 185 MBq and those that received 370 MBq ($P<0.0001$). Boelaert et al compared the effectiveness of 370 MBq with 592 MBq in 1240 patients. They found a much higher success rate in patients that received 592 MBq than 370 MBq group(46).

Patient age is another factor considered to affect the outcome of I-131 therapy. Jensen et al(47) in a retrospective study compared the treatment outcome of two groups of patients: Group 1 with a mean age of 44± 12 years and group 2 with a mean age of 51.3 ± 15.1. They concluded that there is no association between the patient age and the outcome of the therapy as the cure rate in group 1 was 60% and in group 2 was 59%. Schneider et al(45) and Aktas et al(48)showed that elderly patients are more likely to respond well with radioiodine than younger patients in univariate

analysis but Schneider et al reported this association was lost when multivariate analysis was conducted. Again, there are many reports of no association between I-131 success rate with patient's age(28, 39, 49-51), among which is a large population size retrospective study conducted by Metso et al at Tampere University Hospital in Finland(42). Boelaert et al reports female patients had a statistically significant higher success rate compared to males(46). In other studies (26, 31, 42, 52) females tended to have higher success rate but the association was not statistically significant. And other studies showed no association between the patients' gender and treatment outcome (31, 41, 45, 47, 50, 53, 54).

While some studies(42, 45, 49) reported that patients with low 24-hour I-123 uptake prior to administration are likely to have a lower cure rate, others reported no association between the two(28, 39, 50, 55, 56).

Thyroid goiter is associated with poor outcome of I-131 therapy(52) although another study reported no association was found(39). This controversy could be explained by the fact that these studies did not use an objective measurement of the thyroid size; they only used palpation.

The effect of higher pretreatment free T4 levels and Tc-99m uptake on the outcome of I-131 therapy is still controversial. Maha et al conducted a retrospective study to assess the efficacy of 370 MBq and 555 MBq doses of I-131 in Grave's disease patients, they found that higher pretreatment free T4 and Tc-99m uptake were not associated with treatment failure. Alexander et al(57) and Allahabadia et al(52) reports otherwise.

Another factor that has been reported to affect the outcome of I-131 therapy for hyperthyroidism is thyroid receptor antibody level in serum(58). Michelangeli et al (59) in 1995 measured the level of thyroid stimulating antibody (TSab), thyroid blocking antibody (TBab) and TSH binding inhibitory immunoglobulin (TBII) in patients with Grave's disease before and after I-131 therapy and reported that patients who develop early hypothyroidism following I-131 therapy had higher basal TBab level.

Some drugs have been known to alter the effectiveness of radioiodine therapy; one is lithium(60). Vangu and Hammond in their simple randomized experimental cohort study found that patients that receive lithium with I-131 are more likely to achieve successful therapy(61, 62). The effect of steroids has also been studied. They are routinely used to prevent exacerbation of thyroid associated orbithopathy and are known to inhibit the secretion of TSH, decrease peripheral deiodination, decrease the serum level of thyroxine binding globulin and enhance urinary iodine clearance(63). The anti-inflammatory effect with enhanced urinary excretion of Iodine could possibly decrease the effectiveness of radioiodine therapy. However studies have shown that outcome of I-131 therapy is not likely to be influenced by prior administration of steroids. This may be because the steroid dose is not sufficient(47, 64). The effect of smoking on RAI therapy is still unsettled, majority reporting it has no effect(31, 54, 65).

Radioactive iodine therapy for hyperthyroidism at Groote Schuur Hospital dates back to 1965 when I-131 therapy was conducted by the Department of Radiation Oncology in conjunction with Endocrine clinic(66). There has not been review of the effectiveness of the therapy since 2011 when the Nuclear Medicine department took over. This project proposal becomes important to evaluate the success and failure of the current protocol of I-131 therapy.

Research questions

1. In what percentage of patients receiving I-131 therapy was the treatment successful?

2. A) In which patients was the treatment not successful and a second dose needed?
   B) What factors could be responsible for the treatment failure?

Research Methodology

Design

Patients' treatment records from the commencement of Iodine therapy (April 2010) will be retrieved from the Departmental benign therapy records. Missing records may necessitate retrieval of patient's main hospital folder. Tc-99m pertechnetate scans will be reviewed; laboratory results and thyroid ultrasound (if available) of patients who were treated in Nuclear Medicine Department of Groote Schuur Hospital will be retrieved retrospectively.

Data collection

Patients' folder number, gender, age, address, history and examination details will be recorded in a data sheet (Appendix 1). Tc-99m pertechnetate thyroid scan will be retrieved and reprocessed on the Hermes processing station. The researcher will read laboratory results on the National Health Laboratory Service (NHLS) track and the ultrasound reports on the GSH isite enterprise.

Data processing

Both quantitative and qualitative data will be entered in the excel spreadsheet. Excel and SPSS package will be used for the descriptive statistical tests.

Research limitations

Only the researcher will be involved in interpreting the Nuclear Medicine scan in addition to the retrospective nature of the study.

Ethical Issues

Patients' details used in the study will only be available to individuals involved in the study and will be properly stored; As prescribed by Helsinki declaration(67), no patients' detail will be used in the final report and patients' confidentiality will be maintained throughout the study.

Funding:

As no further images or blood investigations will be carried out, no further cost to the patient or hospital for this study is expected. The cost of stationaries, photocopying and printing will be borne by the researcher.

References

1. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American thyroid association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid : official journal of the American Thyroid Association. 2016;26(10):1343-421.
2. Cooper DS. Hyperthyroidism. Lancet (London, England). 2003;362(9382):459-68.
3. Sarkar SD, editor Benign thyroid disease: what is the role of nuclear medicine? Seminars in nuclear medicine; 2006: Elsevier.
4. Pearce EN. Diagnosis and management of thyrotoxicosis. BMJ : British Medical Journal. 2006;332(7554):1369-73.
5. Kang AS, Grant CS, Thompson GB, van Heerden JA. Current treatment of nodular goiter with hyperthyroidism (Plummer's disease): surgery versus radioiodine. Surgery. 2002;132(6):916-23.
6. Liu J, Fu J, Xu Y, Wang G. Antithyroid Drug Therapy for Graves' Disease and Implications for Recurrence. International journal of endocrinology. 2017;2017:3813540.
7. Becker DV, Sawin CT, editors. Radioiodine and thyroid disease: the beginning. Seminars in nuclear medicine; 1996: Elsevier.
8. Bonnema SJ, Hegedüs L. Radioiodine therapy in benign thyroid diseases: effects, side effects, and factors affecting therapeutic outcome. Endocrine reviews. 2012;33(6):920-80.
9. Wyszomirska A. Iodine-131 for therapy of thyroid disease. Physical and biological basis. Nuclear medicine Review. 2012;15(2):120-3.
10. Cayir D, Araz M. Radioiodine Therapy of Benign Thyroid Diseases. International Journal. 2017;4(1):7.
11. Ma C, Xie J, Wang H, Li J, Chen S. Radioiodine therapy versus antithyroid medications for Graves' disease. The Cochrane database of systematic reviews. 2016;2:Cd010094.
12. Mumtaz M, Lin LS, Hui KC, Khir ASM. Radioiodine I-131 for the therapy of Graves' disease. The Malaysian journal of medical sciences: MJMS. 2009;16(1):25.
13. Santos RB, Romaldini JH, Ward LS. Propylthiouracil reduces the effectiveness of radioiodine treatment in hyperthyroid patients with Graves' disease. Thyroid : official journal of the American Thyroid Association. 2004;14(7):525-30.
14. Tuttle RM, Patience T, Budd S. Treatment with propylthiouracil before radioactive iodine therapy is associated with a higher treatment failure rate than therapy with radioactive iodine alone in Graves' disease. Thyroid : official journal of the American Thyroid Association. 1995;5(4):243-7.
15. Ghadban WK, Zirie MA, Al-Khateeb DA, Jayyousi AA, Mobayedh HM, El-Aloosy AS. Radioiodine treatment of hyperthyroidism. Success rate and influence of thyrostatic medication. Saudi medical journal. 2003;24(4):347-51.
16. Connell JM, Hilditch TE, McCruden DC, Robertson J, Alexander WD. Effect of pretreatment with carbimazole on early outcome following radio-iodine (131I) therapy. European journal of nuclear medicine. 1984;9(10):464-6.
17. Braga M, Walpert N, Burch HB, Solomon BL, Cooper DS. The effect of methimazole on cure rates after radioiodine treatment for Graves' hyperthyroidism: a randomized clinical trial. Thyroid : official journal of the American Thyroid Association. 2002;12(2):135-9.

18. Bonnema SJ, Bennedbæk FN, Veje A, Marving J, Hegedüs L. Propylthiouracil before 131I Therapy of Hyperthyroid Diseases: Effect on Cure Rate Evaluated by a Randomized Clinical Trial. The Journal of Clinical Endocrinology & Metabolism. 2004;89(9):4439-44.
19. Hancock LD, Tuttle RM, LeMar H, Bauman J, Patience T. The effect of propylthiouracil on subsequent radioactive iodine therapy in Graves' disease. Clin Endocrinol (Oxf). 1997;47(4):425-30.
20. Bazzi MN, Bagchi N. Adjunctive treatment with propylthiouracil or iodine following radioiodine therapy for Graves' disease. Thyroid : official journal of the American Thyroid Association. 1993;3(4):269-72.
21. National Regulator Act. 1999 Act 47 of 1999, and regulations.
22. Kahaly GJ, Dillmann WH. Thyroid hormone action in the heart. Endocrine reviews. 2005;26(5):704-28.
23. Stokkel MP, Junak DH, Lassmann M, Dietlein M, Luster M. EANM procedure guidelines for therapy of benign thyroid disease. European journal of nuclear medicine and molecular imaging. 2010;37(11):2218-28.
24. Erem C, Kandemir N, Hacihasanoglu A, Ersoz HO, Ukinc K, Kocak M. Radioiodine treatment of hyperthyroidism: prognostic factors affecting outcome. Endocrine. 2004;25(1):55-60.
25. Sztal-Mazer S, Nakatani VY, Bortolini LG, Boguszewski CL, Graf H, de Carvalho GA. Evidence for higher success rates and successful treatment earlier in Graves' disease with higher radioactive iodine doses. Thyroid : official journal of the American Thyroid Association. 2012;22(10):991-5.
26. Nordyke RA, Gilbert FI. Optimal iodine-131 dose for eliminating hyperthyroidism in Graves' disease. Journal of Nuclear Medicine. 1991;32(3):411-6.
27. Vanderpump MP, Ahlquist JA, Franklyn JA, Clayton RN. Consensus statement for good practice and audit measures in the management of hypothyroidism and hyperthyroidism. The Research Unit of the Royal College of Physicians of London, the Endocrinology and Diabetes Committee of the Royal College of Physicians of London, and the Society for Endocrinology. BMJ : British Medical Journal. 1996;313(7056):539-44.
28. Catargi B, Leprat F, Guyot M, Valli N, Ducassou D, Tabarin A. Optimized radioiodine therapy of Graves' disease: analysis of the delivered dose and of other possible factors affecting outcome. European journal of endocrinology. 1999;141(2):117-21.
29. Nakajo M, Tsuchimochi S, Tanabe H, Nakabeppu Y, Jinguji M. Three basic patterns of changes in serum thyroid hormone levels in Graves' disease during the one-year period after radioiodine therapy. Annals of nuclear medicine. 2005;19(4):297-308.
30. Canto AU, Dominguez PN, Jimeno CA, Obaldo JM, Ogbac RV. Comparison of Fixed versus Calculated Activity of Radioiodine for the Treatment of Graves Disease in Adults. Endocrinology and Metabolism. 2016;31(1):168-73.
31. Miranda-Padua ML, Cunanan EC, Kho SA, Marcelo M, Torres JF, Monzon OP. A randomized double-blind comparison of fixed versus calculated radioiodine dose in the treatment of Graves' hyperthyroidism. Philipp J Intern Med. 2014;52(52):1-7.
32. Jacob JJ, Stephen C, Paul TV, Thomas N, Oommen R, Seshadri MS. No impact of dietary iodine restriction in short term development of hypothyroidism following fixed dose radioactive iodine therapy for Graves' disease. Indian J Endocrinol Metab. 2015;19(1):60-5.

33. Husseni MA. The Incidence of Hypothyroidism Following the Radioactive Iodine Treatment of Graves' Disease and the Predictive Factors Influencing its Development. World J Nucl Med. 2016;15(1):30-7.
34. Ahmad AM, Ahmad M, Young ET. Objective estimates of the probability of developing hypothyroidism following radioactive iodine treatment of thyrotoxicosis. Eur J Endocrinol. 2002;146(6):767-75.
35. Khalid Y, Barton D, Baskar V, Kumar H, Jones P, West T, et al. Efficacy of Fixed High Dose Radioiodine Therapy for Hyperthyroidism-a 14 year Experience: A focus on Influence of Pre-treatment Factors on Outcomes. British Journal of Medical Practitioners. 2011;4(3).
36. V Toh HS. Effectiveness Of Fixed Dose Radioactive Iodine (Rai) For The Treatment Of Thyrotoxicosis: A United Kingdom District General Hospital Experience. . Internet Journal Of Endocrinology. 2008;5(2).
37. Yau JS, Chu K, Li JK, Chan K, Lau I, Yum S, et al. Usage of a fixed dose of radioactive iodine for the treatment of hyperthyroidism: one-year outcome in a regional hospital in Hong Kong. Hong Kong Med J 2009;15:267-73.
38. Enyi Ejeh MJ, Omotayo Ogunjobi K, Enyi Ejeh J, Solomon Adedapo K, J FE. Effectiveness of Fixed Dose Radioactive Iodine (RAI) for the Treatment of Hyperthyroidism: Experience of a Teaching Hospital in South West Nigeria. Molecular imaging and radionuclide therapy. 2013;22(2):36-41.
39. Kita T, Yokoyama K, Kinuya S, Taki J, Michigishi T, Tonami N. Single dose planning for radioiodine-131 therapy of Graves' disease. Annals of nuclear medicine. 2004;18(2):151-5.
40. JARLØV AE, NYGAARD B, HEGEDÜS L, HARTLING SG, HANSEN JM. Observer variation in the clinical and laboratory evaluation of patients with thyroid dysfunction and goiter. Thyroid : official journal of the American Thyroid Association. 1998;8(5):393-8.
41. Shinto A, Pachen L, Sreekanth T. Fixed dose radioactive iodine therapy in hyperthyroidism-outcome and factors affecting it in a region in South India. Thyroid Research and Practice. 2010;7(3):84.
42. Metso S, Jaatinen P, Huhtala H, Luukkaala T, Oksala H, Salmi J. Long‐term follow‐up study of radioiodine treatment of hyperthyroidism. Clinical endocrinology. 2004;61(5):641-8.
43. Cooper T, Traub A, Magennis S, Nevin N, Darzi A, Kelly C, et al. Irish endocrine society. Irish Journal of Medical Science. 1986;155(9):335-42.
44. Allahabadia A, Daykin J, Sheppard MC, Gough SC, Franklyn JA. Radioiodine treatment of hyperthyroidism—prognostic factors for outcome. The Journal of Clinical Endocrinology & Metabolism. 2001;86(8):3611-7.
45. Schneider DF, Sonderman PE, Jones MF, Ojomo KA, Chen H, Jaume JC, et al. Failure of Radioactive Iodine in the Treatment of Hyperthyroidism. Annals of Surgical Oncology. 2014;21(13):4174-80.
46. Boelaert K, Manji N, Sheppard M, Gough S, Franklyn J. Using an increased fixed dose of 131 I (600MBq) leads to improved outcome in patients with hyperthyroidism. Endocrine Abstracts. 2007.
47. Jensen BE, Bonnema SJ, Hegedüs L. Glucocorticoids do not influence the effect of radioiodine therapy in Graves' disease. European journal of endocrinology. 2005;153(1):15-21.

48. Aktas GE, Turoglu HT, Erdil TY, Inanir S, Dede F. Long-Term Results of Fixed High-Dose I-131 Treatment for Toxic Nodular Goiter: Higher Euthyroidism Rates in Geriatric Patients. Molecular imaging and radionuclide therapy. 2015;24(3):94-9.
49. Grosso M, Traino A, Boni G, Banti E, Porta MD, Manca G, et al. Comparison of different thyroid committed doses in radioiodine therapy for Graves' hyperthyroidism. Cancer biotherapy & radiopharmaceuticals. 2005;20(2):218-23.
50. Jaiswal AK, Bal C, Damle NA, Ballal S, Goswami R, Hari S, et al. Comparison of clinical outcome after a fixed dose versus dosimetry-based radioiodine treatment of Graves' disease: Results of a randomized controlled trial in Indian population. Indian journal of endocrinology and metabolism. 2014;18(5):648.
51. Quinon A, Oabel E, Jimeno C. Clinical factors affecting the outcome in postradioactive iodine (RAI) therapy patients-Philippine Heart Center experience. World Journal of Nuclear Medicine. 2007;6(suppl. 1):S41.
52. Allahabadia A, Daykin J, Holder RL, Sheppard MC, Gough SC, Franklyn JA. Age and gender predict the outcome of treatment for Graves' hyperthyroidism. The Journal of Clinical Endocrinology & Metabolism. 2000;85(3):1038-42.
53. Aktaş GE, Turoğlu HT, Erdil TY, İnanır S, Dede F. Long-Term Results of Fixed High-Dose I-131 Treatment for Toxic Nodular Goiter: Higher Euthyroidism Rates in Geriatric Patients. Molecular imaging and radionuclide therapy. 2015;24(3):94.
54. Lewis A, Atkinson B, Bell P, Courtney H, McCance D, Mullan K, et al. Outcome of 131I therapy in hyperthyroidism using a 550MBq fixed dose regimen. The Ulster medical journal. 2013;82(2):85.
55. Leslie WD, Ward L, Salamon EA, Ludwig S, Rowe RC, Cowden EA. A randomized comparison of radioiodine doses in Graves' hyperthyroidism. The Journal of Clinical Endocrinology & Metabolism. 2003;88(3):978-83.
56. Kok S, Smit J, De Craen A, Goslings B, Van Eck-Smit B, Romijn J. Clinical outcome after standardized versus dosimetric radioiodine treatment of hyperthyroidism: an equivalence study. Nuclear medicine communications. 2000;21(11):1071-8.
57. Alexander EK, Larsen PR. High dose 131I therapy for the treatment of hyperthyroidism caused by Graves' disease. The Journal of Clinical Endocrinology & Metabolism. 2002;87(3):1073-7.
58. Atkinson S, McGregor AM, Kendall-Taylor P, Peterson MM, Smith BR. Effect of radioiodine on stimulatory activity of Graves' immunoglobulins. Clin Endocrinol (Oxf). 1982;16(6):537-43.
59. Michelangeli VP, Poon C, Topliss DJ, Colman PG. Specific effects of radioiodine treatment on TSAb and TBAb levels in patients with Graves' disease. Thyroid : official journal of the American Thyroid Association. 1995;5(3):171-6.
60. Kessler L, Palla J, Baru JS, Onyenwenyi C, George AM, Lucas BP. Lithium as an adjunct to radioactive iodine for the treatment of hyperthyroidism: a systematic review and meta-analysis. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2014;20(7):737-45.
61. Hammond EN. Effect of adjuvant lithium on thyroxine (T4) concentration after radioactive iodine therapy. European journal of nuclear medicine and molecular imaging. 2016;43(11):1980-7.
62. Hammond ENB, Vangu M-D-THW. Lithium-enhanced radioactive iodine ablation of hyperthyroid patients. Journal of Endocrinology, Metabolism and Diabetes of South Africa. 2016;21(3):51-5.

63. RG D. The Adrenal cortex in hypothyroidism. Werner & Ingbar's the thyroid- a fundamental and clinical text. Philadelphia: Lippincott & Wilkins
; 2005.
64. Bogazzi F, Bartalena L, Brogioni S, Scarcello G, Burelli A, Campomori A, et al. Comparison of radioiodine with radioiodine plus lithium in the treatment of Graves' hyperthyroidism. The Journal of Clinical Endocrinology & Metabolism. 1999;84(2):499-503.
65. Sagel J, Epstein S, Kalk J, Van Mieghem W. Radioactive iodine (131I) therapy for thyrotoxicosis at Groote Schuur Hospital over a 6-year period. Postgraduate medical journal. 1972;48(559):308-13.
66. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. The Journal of the American College of Dentists. 2014;81(3):14-8.

2.0 PUBLICATION READY MANUSCRIPT -

Full title: Efficacy of single fixed dose of radioiodine (I-131) therapy in patients treated for hyperthyroidism at Nuclear Medicine Department of Groote Schuur Hospital (GSH).

Authors:

Ahmed Rufai Isah[1], MBBS

Tessa Kotze[1], MBCH, FCNP

Nuclear Medicine Division, Department of Radiation Medicine, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa

Correspondence:

Ahmed Rufai Isah

Nuclear Medicine Division

C3/C4, New Main Building, Groote Schuur Hospital

Anzio Road, Observatory

Cape Town 7925

South Africa

Email: ahmadunkarofi@yahoo.com; ahmed.isah@uct.ac.za

Tel: (+27) 21 404 4003; (+27) 61 6029064

Conflict of interest: None

2.1 ABSTRACT

Aim:

The aims of this audit were:

To determine the proportion of hyperthyroid patients receiving I-131 therapy in whom treatment with a single fixed dose was successful, as defined by the achievement of euthyroidism or hypothyroidism 6-months after the therapy;

To identify patients in whom treatment was not successful and a second dose needed;

And, if possible, to establish the factors associated with treatment failure.

Methods:

A single observer reviewed the records of all patients who received I-131 therapy for hyperthyroidism between 23rd April 2010 and 23rd November 2017 in conjunction with their pre and post treatment thyroid function tests. Results of their thyroid ultrasound were retrieved and documented. The images of their Tc-99m sodium pertechnetate thyroid scans were also retrieved and reprocessed.

Results:

The records of 409 patients treated between April 2010 and November 2017 were retrieved. 223 (63%) patients were referred by the endocrine clinic at Groote Schuur hospital (GSH. Of the 409 patients, 56 (14%) patients that were excluded because their post therapy records were not available for analysis.

Majority of our patients were females 310 (88%). Patients between the ages of 15 and 45 years are more likely to present with Grave's disease while those aged more than 45 years presented with toxic multinodular gland (p=0.000). Patients that presented between the ages of 15 and 45 years are more likely to have moderately increased pretreatment FT4 (12-51 mmol/L) (p=0.002). We administered a radioiodine therapy dose of 456.6±54.8 MBq (Mean ± SD) to these 409 patients. Among the 353 patients, with complete records, 314(89%) achieved cure at some stage after receiving one

dose of RAI; 239(76%) achieving cure ≤ 6 months of therapy and 75(24%) patients after 6 months.

In our audit the patients who failed to achieve cure following the first RAI therapy appeared to be younger (median(interquartile range) age 39(16), p= 0.03), have severe hyperthyroidism as demonstrated by higher pre-treatment FT4 (median(interquartile range) 27 pmol/L(30.6), p= 0.05) and high pertechnetate uptake (median(interquartile range) uptake 9.9%(14), p= 0.002) on thyroid scintigraphy.

CONCLUSION

Our audit showed RAI therapy was found to be successful in 68% of patients at 6 month and 89% at a year. A second therapy with radioactive iodine would be indicated in 32% of patients, as these patients have not achieved cure at 6 months. Patients presenting with severe thyrotoxicity are likely to require more than one RAI therapy. Due to major deficiencies in referral, record keeping and follow up, other factors responsible for treatment were not be able to be evaluated.

Based on these findings, suggested areas for further research are: should patients with severe hyperthyroidism be considered for pretreatment with antithyroid medication prior to RAI; would a one year follow up after radioiodine therapy be considered before second RAI.

Now that the deficiencies in our current practice have been identified and suggestions put forward to address these deficiencies, a follow up audit would be needed.

Key words: Hyperthyroidism, I-131 (Radioiodine) therapy, Effectiveness.

2.2 MAIN MANUSCRIPT

Introduction

Iodine-131 (I-131) has been successfully used in the treatment of hyperthyroidism for more than 70 years and is now recommended as a first line treatment in some forms of thyrotoxicosis (1). Its history dates to 1936 when Saul Hertz asked Karl Compton, during a lecture presentation by the latter at Harvard Medical School, if radioactive iodine could be produced. This question triggered a series of work that led to the production of I-131, the radionuclide that is used today. I-131 was first used in a human to treat hyperthyroidism on October 12, 1941 by Hamilton and Beck(2).

Cayir et al(3); in their recent systemic review on the use of radioiodine in benign thyroid disease, concluded that treatment of hyperthyroidism with I-131 is a safe and cost effective alternative to surgery and medical therapy. Chao et al(4) reported in 2015 that the recurrence of hyperthyroidism is less likely in patients that receive I-131 when compared with patients that receive antithyroid drugs (ATD's). There are two approaches to the administration of radioiodine, a fixed dose or a calculated dose. There is no difference in the therapeutic outcomes however with the calculated dose more investigations are needed with increasing complexity and cost (3, 5-8).

The adverse effects that have been associated with the use of I-131 are either due to a transient exacerbation of hyperthyroid symptoms from radiation thyroiditis or extra thyroidal such as worsening of thyroid orbithopathy, sialadenitis, immunogenic effects, teratogenicity and carcinogenicity (9, 10). Radioiodine therapy is contraindicated in pregnancy, lactation, patients with a thyroid nodule suspicious of thyroid cancer and patients that are unable to comply with radiation safety guidelines (1).

Radioactive iodine therapy for hyperthyroidism at GSH dates back to 1965 when I-131 therapy was conducted by the Department of Radiation Oncology in conjunction with Endocrine clinic(11). Since 2011, the Nuclear Medicine Department of GSH has been conducting radioiodine therapy (RAI) for patients referred with hyperthyroidism by the Endocrine Unit of the hospital and other sites. There has not been a review of the

effectiveness of the therapy. The Nuclear Medicine department has used the single fixed dose method of RAI administration in the management of hyperthyroidism.

The aims of this audit were:

- To determine the proportion of hyperthyroid patients receiving I-131 therapy in whom treatment with a single fixed dose was successful, as defined by achievement of euthyroidism or hypothyroidism 6-months after the therapy;
- To identify patients in whom treatment was not successful and a second dose needed;
- And, if possible, to establish the factors associated with treatment failure.

Methods

All the Nuclear Medicine Department patient treatment records of Iodine therapy between April 2010 and November 2017 were retrieved. A separate Departmental attendance register was checked to identify patients who received I-131. Patients receiving treatment for thyroid cancer were excluded.

The patient treatment records included, for each visit, the history, physical examination findings, results of investigations, diagnosis and therapy. GSH patients who required I-131 therapy were discussed telephonically by the registrars of Nuclear Medicine and Endocrine Units. There was not a formal referral letter for every patient. Our policy during the course of this study (April 2010 to November 2017) was to withdraw antithyroid medication five days prior to I-131 administration and schedule a first follow up visit in Endocrine clinic six weeks post I-131 administration.

The protocol included a Tc-99m sodium pertechnetate thyroid scan to confirm uptake by the thyroid gland and thyroid ultrasound to characterize any suspicious areas before the therapy dose was given.

The thyroid scintigraphy images were acquired using Tc-99m sodium pertechnetate. Adults received approximately 100MBq Tc-99m sodium pertechnetate while paediatric doses were calculated based on the EANM dosage card (version 1.5.2008). Either a Siemens ecam signature series dual head gamma camera or a Symbia hybrid SPECT-CT system (Siemens Medical Solutions) was used to acquire static images using low energy high resolution (LEHR) and pinhole collimators for 10 minutes duration each. The raw data images were stored in the Departmental electronic archive Hermes processing station (Hermes Gold P5 type, version 4.15).

The dose of I-131 was administered orally in the therapy room in the Nuclear Medicine Department after contraindications had been excluded and thyroid scintigraphy had confirmed uptake by the thyroid. The patient was allowed to leave the department when the level of radiation being emitted has dropped to a safe level ($\leq 25\mu Sv/hr$ at 1 meter according to South African legislation).

Patient follow up was done by the respective referring physician. The first thyroid function test was done within 8-weeks after radioiodine administration and subsequently at 2 to 3 monthly intervals.

Three consecutive thyroid function tests were used to identify patients who had achieved cure (euthyroid or hypothyroid status 6 months after therapy).

Data collection

Data collection took place between January and July 2018. The available information on each patient was recorded on a data sheet (Appendix 1); the folder number, gender, date of birth, address, history, Tc-99m sodium pertechnetate thyroid scan results (after the raw data had been retrieved from Nuclear Medicine Division's electronic image archive (GSH Hermes archive) and reprocessed), thyroid ultrasound report (retrieved from the GSH Isite enterprise) and all the laboratory results on the National Health Laboratory Service (NHLS) track. Items not present in the treatment records and results which could not be traced were considered to be missing data and recorded on the data collection sheets as NR (not recorded).

Data processing

Data was entered into an Excel spreadsheet. Excel (Microsoft Office 2011) and SPSS package version 25, 2017 were used for the descriptive statistical tests. Baseline data is presented as frequencies or median and interquartile range if not normally distributed. $\chi 2$ – test and Mann- Whitney U- test (where appropriate) were used for statistical analysis.

Two limitations were identified: The first being the retrospective nature of the study and the second only the researcher was involved in interpreting the Nuclear Medicine scans.

The Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town, duly approved the study. HREC REF: 072/2018.

RESULTS

The records of 409 patients treated between April 2010 and November 2017 were retrieved. From our records 223 (63.%) patients were referred by the endocrine clinic of Groote Schuur Hospital. Many important components of the patients' history and examination were not available for evaluation. That included; whether the patients had hypertension, cardiac disease, diabetes and eye signs which were not recorded in 69%, 95.2%, 88.7% and 70.3% respectively as shown in table 1. In addition, important information that is reported in the literature to affect the outcome of RAI therapy was also not available for evaluation. Examples of these variables are duration of treatment with carbimazole, findings on neck palpation and ultrasound findings, as shown in table 2.

Of the 409 patients that received a single fixed dose of I-131 therapy within the period under review, 56 (14%) were excluded, among this, 6 patients were referred from

private and their post therapy blood results were not available while the remaining 50 patients were lost to follow up leaving 353(86%) for analysis.

Majority of our patients are females 310 (88%). For analysis, patients were divided into those less than 15 years, 15 to 45 years and more than 45 years at presentation. Patients between the ages of 15 to 45 years are more likely to present with Grave's disease than older patients (p=0.000) and are more likely to have moderately high pretreatment FT4 of between 12 to 51mmol/L(p=0.002). While the older patients (>45 years) are more likely to present with TMG (p=0.000). The rest of the demographic, clinical and laboratory characteristics of our patients at presentation are summarized in table 1 and 3.

Of these 353 patients, 314(89%) patients achieved cure at some stage after receiving one dose of RAI. Of the 314 patients, 239(76%) achieved cure ≤ 6 months of therapy and 75(24%) patients after 6 months. We administered a radioiodine therapy dose of 456.6±54.8 MBq (Mean ± SD) to all 353 patients.

Of the 39 patients that remained hyperthyroid one year after receiving their first therapy dose, 22 patients were referred back and received a second dose of RAI therapy. Of these 22 patients, 20 patients achieved cure after the second therapy dose. The remaining 2 were still hyperthyroid at 7 and 9 months respectively after the second RAI therapy dose.

Our audit suggested that, among the patients that were adequately followed up, those that failed the first RAI therapy were younger (median age 39(interquartile range 16) p= 0.03), had more marked hyperthyroidism as demonstrated by higher pre-treatment FT4 (median(interquartile range) 27 pmol/L(30.6), p= 0.05)and high pertechnetate uptake (median(interquartile range) uptake 9.9%(14), p= 0.002)on thyroid scintigraphy.

DISCUSSION

Our audit showed major deficiencies in referral, record keeping and follow up. In many of our patients there were several clinical variables that were not available. The practice during the time covered by the audit was to discuss the referral of the patient between endocrinology and nuclear medicine telephonically. This may have resulted in information not being elicited from the referring physicians or not documented during the telephonic conversation. Examples are a history of hypertension, diabetes, cardiac diseases and the duration of carbimazole treatment. In addition, clinical and laboratory findings were not completed by the nuclear physician during the evaluation at the time of the therapy. This included thyroid size (enlarged/not enlarged); thyroid consistency on palpation and whether a thyroid ultrasound had been done. There are reports that these variables affect the outcome of radioiodine therapy (9, 12, 13). This meant we had insufficient data to evaluate the effect of clinical and biochemical findings on the outcome of the therapy.

In addition there were 56 (14%) patients that were lost to follow up. This group had to be excluded in our analysis.

This audit has been invaluable in identifying the weaknesses in current practice. The findings of this audit are being used to improve referral systems, record keeping and follow up of these patients. With regards to the referral system, a template of the pertinent information should be available. This should include the date of diagnosis, previous medical history, duration of treatment with anti-thyroid drugs and baseline and summary of the laboratory tests done. This should be available to both referring physicians and nuclear medicine physicians. When the patient is seen prior to the administration of RAI by the nuclear physicians a more detailed user-friendly treatment form may be helpful. The data sheet used for this study could serve as a good template.

The mean dose of 457 MBq used was within the range of 370MBq to 555MBq as recommended by ATA guideline(1) and resulted in a euthyroid or hypothyroid state in

68% of the 353 patients with adequate follow up at 6 months and 89% at a year. Our findings at 6 months are comparable to those reported by Allahabadia et al, Leslie et al and Alexander et al (14-16). This result is higher than the 63% reported by Yau et al(17) and the same as 68% in those who received only RAI in Hammond et al(18). It is important to take note of the fact that follow up was lost in 14% of our patients. These findings do however raise the question, is 3 months too early to perform a second radioactive iodine therapy or should this decision be delayed for 1 year. This need further research to validate this finding.

Our audit suggests that failure of RAI is more likely in patients that are younger than 39 years with severe hyperthyroidism, as demonstrated by higher pre-treatment FT4 and higher pertechnetate uptake. This is consistent with reports in the literature (7, 19-21). The failure of radioiodine activity in patients with severe hyperthyroidism may be attributed to the high I-131 turnover in the thyroid tissue with a shorter transit time as described recently by Zhang et al in China(22). This finding suggests delaying RAI therapy in severely thyrotoxic patients and using anti thyroid medication until thyrotoxicosis is moderately controlled. However the delay should not be so long as to cause radio resistance, as reported by Shivaprasad et al(23)

Our data showed the majority of the patients had Grave's disease (53%). This could possibly explain why there was no association between the type of hyperthyroidism and RAI failure, as has been previously reported (12, 24, 25).

Some of the limitations of this study is its retrospective design. Retrospective studies are prone to misclassification bias. The studies are subject to confounding factors. With a retrospective study, one cannot determine causation, only association and has been the case in this study, key statistics cannot be measured. It is also difficult to assess temporal relationship.

An additional limitation is the large number of missing data that did not allow comprehensive analysis. The result been factors which are reported to influence the treatment outcome could net be evaluated in this study.

CONCLUSION

In this study, the RAI therapy of patients with hyperthyroidism that received RAI therapy in Nuclear Medicine Department at Groote Schuur Hospital from April 2010 to November 2017 was audited.

In patients who were followed up, RAI therapy was found to be successful in 68% of patients at 6 month and 89% at a year. A second therapy with radioactive iodine would be indicated in 32% of patients, as these patients have not achieved cure at 6 months. Patients presenting with severe thyrotoxicity are likely to require more than one RAI therapy. Due to major deficiencies in referral, record keeping and follow up, other factors responsible for treatment were not be able to be evaluated.

Based on these findings, suggested areas for further research are: should patients with severe hyperthyroidism be considered for pretreatment with antithyroid medication prior to RAI; would a one year follow up after radioiodine therapy be considered before second RAI.

Now that the deficiencies in our current practice have been identified and suggestions put forward to address these deficiencies, a follow up audit would be needed.

2.4 References

1. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American thyroid association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid : official journal of the American Thyroid Association. 2016;26(10):1343-421.
2. Becker DV, Sawin CT, editors. Radioiodine and thyroid disease: the beginning. Seminars in nuclear medicine; 1996: Elsevier.
3. Cayir D, Araz M. Radioiodine Therapy of Benign Thyroid Diseases. International Journal. 2017;4(1):7.
4. Ma C, Xie J, Wang H, Li J, Chen S. Radioiodine therapy versus antithyroid medications for Graves' disease. The Cochrane database of systematic reviews. 2016;2:Cd010094.
5. Catargi B, Leprat F, Guyot M, Valli N, Ducassou D, Tabarin A. Optimized radioiodine therapy of Graves' disease: analysis of the delivered dose and of other possible factors affecting outcome. European journal of endocrinology. 1999;141(2):117-21.
6. Nakajo M, Tsuchimochi S, Tanabe H, Nakabeppu Y, Jinguji M. Three basic patterns of changes in serum thyroid hormone levels in Graves' disease during the one-year period after radioiodine therapy. Annals of nuclear medicine. 2005;19(4):297-308.
7. Canto AU, Dominguez PN, Jimeno CA, Obaldo JM, Ogbac RV. Comparison of Fixed versus Calculated Activity of Radioiodine for the Treatment of Graves Disease in Adults. Endocrinology and Metabolism. 2016;31(1):168-73.
8. Miranda-Padua ML, Cunanan EC, Kho SA, Marcelo M, Torres JF, Monzon OP. A randomized double-blind comparison of fixed versus calculated radioiodine dose in the treatment of Graves' hyperthyroidism. Philipp J Intern Med. 2014;52(52):1-7.
9. Bonnema SJ, Hegedüs L. Radioiodine therapy in benign thyroid diseases: effects, side effects, and factors affecting therapeutic outcome. Endocrine reviews. 2012;33(6):920-80.
10. Mumtaz M, Lin LS, Hui KC, Khir ASM. Radioiodine I-131 for the therapy of Graves' disease. The Malaysian journal of medical sciences: MJMS. 2009;16(1):25.
11. Sagel J, Epstein S, Kalk J, Van Mieghem W. Radioactive iodine (131I) therapy for thyrotoxicosis at Groote Schuur Hospital over a 6-year period. Postgraduate medical journal. 1972;48(559):308-13.
12. Jensen BE, Bonnema SJ, Hegedüs L. Glucocorticoids do not influence the effect of radioiodine therapy in Graves' disease. European journal of endocrinology. 2005;153(1):15-21.
13. Braga M, Walpert N, Burch HB, Solomon BL, Cooper DSJT. The effect of methimazole on cure rates after radioiodine treatment for Graves' hyperthyroidism: a randomized clinical trial. 2002;12(2):135-9.
14. Leslie WD, Ward L, Salamon EA, Ludwig S, Rowe RC, Cowden EA. A randomized comparison of radioiodine doses in Graves' hyperthyroidism. The Journal of Clinical Endocrinology & Metabolism. 2003;88(3):978-83.
15. Allahabadia A, Daykin J, Sheppard MC, Gough SC, Franklyn JA. Radioiodine treatment of hyperthyroidism—prognostic factors for outcome. The Journal of Clinical Endocrinology & Metabolism. 2001;86(8):3611-7.

16. Alexander EK, Larsen PR. High dose 131I therapy for the treatment of hyperthyroidism caused by Graves' disease. The Journal of Clinical Endocrinology & Metabolism. 2002;87(3):1073-7.
17. Yau JS, Chu K, Li JK, Chan K, Lau I, Yum S, et al. Usage of a fixed dose of radioactive iodine for the
treatment of hyperthyroidism: one-year outcome in
a regional hospital in Hong Kong. Hong Kong Med J 2009;15:267-73.
18. Hammond EN. Effect of adjuvant lithium on thyroxine (T4) concentration after radioactive iodine therapy. European journal of nuclear medicine and molecular imaging. 2016;43(11):1980-7.
19. Bruin Td, Croon CD, Klerk Jd, Isselt Jv. Standardized radioiodine therapy in Graves' disease: the persistent effect of thyroid weight and radioiodine uptake on outcome. Journal of internal medicine. 1994;236(5):507-13.
20. Reinhardt MJ, Joe A, von Mallek D, Zimmerlin M, Manka-Waluch A, Palmedo H, et al. Dose selection for radioiodine therapy of borderline hyperthyroid patients with multifocal and disseminated autonomy on the basis of 99mTc-pertechnetate thyroid uptake. European Journal of Nuclear Medicine and Molecular Imaging. 2002;29(4):480-5.
21. Peters H, Fischer C, Bogner U, Reiners C, Schleusener H. Radioiodine therapy of Graves' hyperthyroidism: standard vs. calculated 131 iodine activity. Results from a prospective, randomized, multicentre study. European journal of clinical investigation. 1995;25(3):186-93.
22. Zhang R, Tan J, Wang R, Zhang G, Jia Q, Meng Z, et al. Analysis of risk factors of rapid thyroidal radioiodine-131 turnover in Graves' disease patients. Scientific reports. 2017;7(1):8301.
23. Shivaprasad C, Prasanna Kumar KM. Long-term carbimazole pretreatment reduces the efficacy of radioiodine therapy. Indian journal of endocrinology and metabolism. 2015;19(1):84-8.
24. Schneider DF, Sonderman PE, Jones MF, Ojomo KA, Chen H, Jaume JC, et al. Failure of Radioactive Iodine in the Treatment of Hyperthyroidism. Annals of Surgical Oncology. 2014;21(13):4174-80.
25. Aktas GE, Turoglu HT, Erdil TY, Inanir S, Dede F. Long-Term Results of Fixed High-Dose I-131 Treatment for Toxic Nodular Goiter: Higher Euthyroidism Rates in Geriatric Patients. Molecular imaging and radionuclide therapy. 2015;24(3):94-9.

3.0 Appendices:

Tables

Table 1: Distribution of patients' clinical information.

		Number of patients (%)	Not recorded (%)
Gender (n)	Females Males	310 (88) 43 (12)	0
Age (n)	<15 years 15-45 years >45 years	5 (1.4) 148 (41.9) 200 (56.7)	0
Hypertension (n)	Yes	109 (30.9)	244 (69.1)
Cardiac diseases (n)	Atrial fibrillation Angina	8 (2.3) 9 (2.5)	336 (95.2)
Diabetes (n)	Type-1 Type-2	4 (1.0) 36 (10)	313 (88.7)
Eye symptoms (n)	Yes No	55(15.6) 283 (80.2)	15 (4.0)
Smoking (n)	Yes No	115 (32.6) 208 (80.2)	14 (4.0)
Action tremors (n)	Yes No	67 (19) 258 (73.1)	28 (7.9)
Pretreatment heart rate (n)	<60 b/min 61-80 b/min >80 b/min	35 (9.9) 167 (47.3) 143 (40.5)	8 (2.3)
Pretreatment TSH (n)	<2.7 mIU/l 0.27-4.2 mIU/l > 4.2 mIU/l	312 (88.4) 29 (8.2) 6 (1.7)	6 (1.7)
Pretreatment FT4 (n)	<12pmol/L 12-51 pmol/L >51 pmol/L	34 (9.6) 280 (79.3) 28 (7.9)	11 (3.1)
Pretreatment Pertechnetate thyroid uptake scan (n)	Yes No	343 (97.2) 7 (2.0)	3 (0.8)

Table 2. Showing distribution of missing variables.

Clinical variables	Recorded (%)	Not recorded
Date of commencement of Carbimazole (n)	Yes 2 (0.6)	351 (99.4)
Eye signs (n)	Yes 5 (1.4) No 100 (28.3)	248 (70.3)
Neck palpation Enlarge thyroid Tenderness Consistency	 Yes 177 (50.1), No 41 (11.6) No 3 (0.9) Smooth- Yes 146 (41.4) Firm 69 (19.5) Nodular 5(1.4)	 135 (38.2) 350 (99.2) 133 (37.7)
Ultrasound findings	Yes 11 (3.1) No 46 (13.0)	NR 296 (83.9)

Table 3. The relationship of age with features at presentation

	<15 years	15-44 years	>45 years	Statistical significance (P) of difference between age groups (by x2 test)
Pretreatment FT4 <12 mmol/L 12-51 mmol/L >51 mmol/L	 1 3 1	 20 105 19	 13 172 8	p=0.002
Pretreatment HR <60 b/min 61-80b/min >80b/min	 0 1 4	 13 59 74	 13 172 8	p= 0.01
Diagnosis GD	 4	 103	 82	p= 0.000

TA TMG	0 1	0 45	4 114	

Table-4; Comparison of clinical and laboratory findings of those who were and were not cured of hyperthyroidism within 6 months of receiving a single dose

	Cured with 1 dose	Not cured with 1 dose	Statistical significance (p) of difference between the group that achieved cure and the group that did not within 6 months (χ2- test /U-test)
Gender Number (n) Female Male	 221 28	 31 8	p= 0.09 (χ2- test)
Age (years) Median (Interquartile range)	48 (21)	39 (16)	p=0.03 (U-test)
Pretreatment pulse rate (b/min) Median (Interquartile range)	80.0 (18)	87.0 (20)	p=0.502 (U-test)
Pretreatment TSH (mIU/l) Median (Interquartile range)	0.01 (0.01)	0.01 (0.48)	p=0.06 (U-test)
Pretreatment FT4 (pmol/l) Median (Interquartile range)	24 (15)	27 (30.6)	p=0.05 (U-test)
% Uptake of Tc-99m pertechnatate Median (Interquartile range)	5.6 (8.0)	9.9 (13.8)	p=0.002 (U-test)
Diagnosis GD TA TMG	 136 3 110	 22 0 17	p=0.09 (χ2- -test)

Chart 1 and 2. Comparison of clinical and laboratory findings of those who were and were not cured of hyperthyroidism within 6 months of receiving a single dose

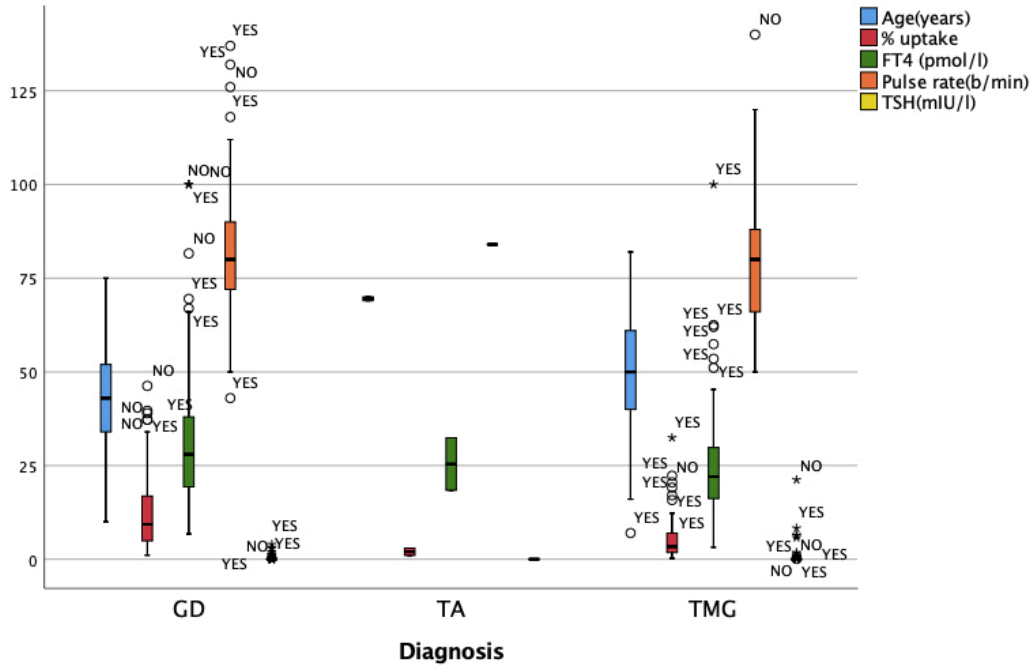
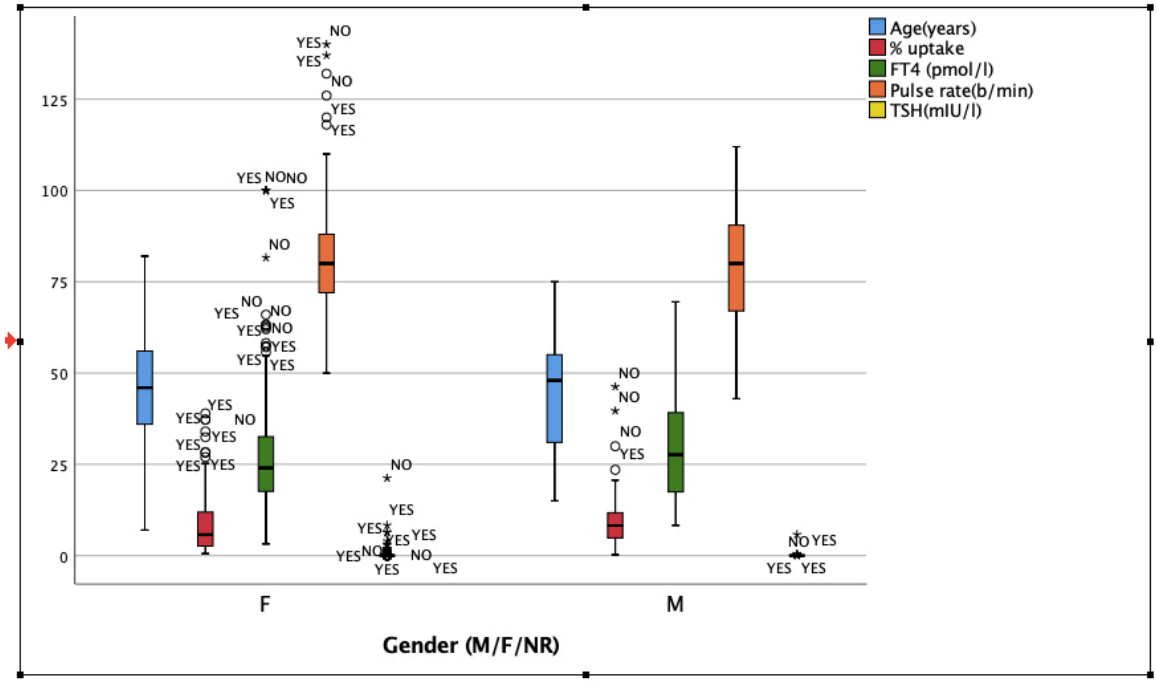


Chart 2



DATA SHEET

Each item must be completed.

1. *If information is not available (e.g. in the clinical notes, or Nuclear medicine, NHLS and radiology archives), it must be entered as no record (NR).*
2. *Dates must be entered as DDMMMYYYY e.g 11 Dec 2017*
3. *Where permitted terms and a box are printed on the Data Sheet, mark the relevant box with X*
4. *NS should only be used when it is printed on the Data sheet and the clinical notes record the accepted term but detail is insufficient; e.g. the clinical notes record the patient as having hypertension but do not state if it is mild, moderate or severe.*
5. *For other permitted terminology check the entries on the **Annotated Data Sheet***
6. *If the terminology in the clinical notes or archives does not conform to a permitted entry, this must be discussed with the supervisor before any further data is collected.*

Demographics

Folder number	
Date form completed	
Date of Diagnosis	
Date of Birth	
Gender	Male □ Female □ NR □
Referred from	GSH □ Other (specify) _____NR □

History

Comorbidities

Hypertension	Mild □ Moderate □ Severe □ NS □ NR □
Cardiac	AF □ MI □ Angina □ NR □
Diabetes	DM 1 □ DM 2 □ NR □

Antithyroid medication

Drug	Date Start	Date Stop
Carbimazole	NR □	NR □
Atenolol	NR □	NR □
Amiodarone	NR □	NR □

Previous radioiodine therapy?

Yes □ No □

If yes: how many? _____

Date	Where given

Eye symptoms of orbithopathy Yes □ No □ NR □

Smoking history Yes □ No □ NR □

Examination

Action tremors Yes □ No □ NR □

Pulse rate (b/min)_____ regular □ not regular □ NR □

Blood Pressure (mmHg) _____ NR □

Eyes signs

NR □ or

Spontaneous retrobulbar pain	Yes □ No □
Pain on attempt up or down gaze	Yes □ No □
Redness of the eyelids	Yes □ No □
Redness of the conjunctiva	Yes □ No □
Swelling of the eyelids	Yes □ No □
Inflammation of the caruncle and plica	Yes □ No □
Conjunctival oedema	Yes □ No □

Total CAS ___/7

Thyroid palpation

Consistency: Soft □ Firm □ Nodules □ NR □

Tenderness: Tender □ not tender □ NR □

Smooth □ NR □

Enlarged □ NR □

^{99m} Tc- Pertechnetate thyroid scans

No □

If Yes

Date_____

Uptake:

Homogeneous Yes □ No □ NR □

Heterogeneous Yes □ No □ NR □

Compared to salivary gland (SG)> SG □ = SG □ <SG □

Additional focal area(s) of increased uptake Yes □ No □ NR □

Number_____ NR □

Additional focal area(s) of decreased uptake Yes □ No □ NR □

Number_____ NR □

Thyroid extends to sternal notch marker Yes □ No □ NR □

% Uptake_____ NR □

Thyroid ultrasound

No □ NR □

If Yes_____

Right lobe present Yes □ No □ NR □

Hyper echoic Yes □ No □ NR □

Hypo echoic Yes □ No □ NR □

Nodularity Yes □ No □ NR □

Size mm(AP x TV)_____ NR □

Left lobe present Yes □ No □ NR □

Hyper echoic Yes □ No □ NR □

Hypo echoic Yes □ No □ NR □

Nodularity Yes □ No □ NR □

Size mm(AP x TV)_____ NR □

Isthmus present Yes □ No □ NR □

Hyper echoic Yes □ No □ NR □

Hypo echoic Yes □ No □ NR □

Nodularity Yes □ No □ NR □

Size mm(AP x TV)_____ NR □

Pre-treatment Blood results (Add rows if necessary)

Date	TSH (mIU/l)	FT4 (pmol/l)	FT3 (pmol/l)

Diagnosis (only one)

Grave's disease_____□
Toxic Multinodular Goiter_____□
Toxic adenoma_____□

Treatment

Date	Dose (MBq)

Activity measured at the level of epigastrium on discharge

At 1 meter (μSv/hr)_____
At 2 meter (μSv/hr)_____

Follow up

Follow up Bloods (add rows if necessary)

	Date	TSH (mIU/l)	FT4 (pmol/l)	FT3 (pmol/l)
1.				
2.				
3.				

Euthyroid state achieved

Yes □ No □ Inadequate follow up □ Date _____

Ethics approval

Appendix removed to avoid exposing officials signature online