



THE OUTCOME OF A CALCULATED
RADIOIODINE DOSE BASED ON
PERTECHNETATE STUDY IN TREATMENT FOR
HYPERTHYROIDISM

by

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DECLARATION

I hereby declare that this research was sent to Universiti Sains Malaysia for the degree of Master of Medicine in Nuclear Medicine. It has not been sent to other universities. With that, this research can be used for consultation and photocopied as reference.

Sincerely,

A handwritten signature in black ink, appearing to read 'Lee Yeong Fong', written over a horizontal line.

Dr Lee Yeong Fong

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ABBREVIATIONS

ATA	American Thyroid Association
ATD	anti-thyroid drugs
CT	Computed Tomography
EANM	European Association of Nuclear Medicine
g	gram
IQR	interquartile range
ITU	radioiodine thyroid uptake ratio
JEPeM	Jawatankuasa Etika Penyelidikan Manusia
keV	kiloelectronvolt
μ Ci	microCurie
μ Ci/g	microCurie per gram
mCi	miliCurie
mg	milligram
mIU/l	mili-International Unit per litre
mls	millilitres
MNG	multinodular goitre
MREC	Medical Research Ethics Committee
MRI	Magnetic Resonance Imaging
mSv/MBq	miliSievert per megaBecquerel
PI	principal investigator
pmol/l	picomole per litre
RAI	radioactive iodine-131
ROI	region of interest
SNMMI	Society of Nuclear Medicine and Molecular Imaging

T3	Triiodothyronine
T4	Tetraiodothyronine/Thyroxine
Tc-99m	Technetium-99m
TcTU	per technetate thyroid uptake ratio
TFT	Thyroid Function Test
TRAb	Thyrotropin receptor antibodies
TSH	Thyrotropin/Thyroid Stimulating Hormone
WHO	World Health Organization

ABSTRAK

Pendahuluan: Iodin radioaktif adalah antara rawatan untuk penyakit hipertiroidisme selain daripada pembedahan dan ubat anti-tiroid. Terdapat dua kaedah yang digunakan secara meluas untuk menentukan dos termasuk dos tetapan dan dos kiraan. Terdapat meta-analisa terkini yang menyokong pengiraan dos adalah lebih baik daripada dos tetapan. Walaubagaimanapun, pengiraan dos dengan kaedah dosimetri atau nisbah pengambilan iodin radioaktif kelenjar tiroid pada 24 jam adalah rumit dan mungkin membebankan pesakit dan pihak hospital. Skan kelenjar tiroid yang menggunakan 'pertechnetate' adalah pengimejan nuklear yang mudah dan boleh diselesaikan pada hari yang sama dan nisbah pengambilan 'pertechnetate' kelenjar tiroid, yang ditentukan daripada skan, boleh digunakan untuk pengiraan dos iodin radioaktif.

Objektif: Tujuan adalah untuk meningkatkan keberkesanan rawatan iodin radioaktif bagi pesakit hipertiroidisme dan kajian ini dilakukan untuk mengukur keberkesanan dos yang dikira berasaskan nisbah pengambilan 'pertechnetate' kelenjar tiroid.

Kaedah: Pesakit hipertiroidisme yang dirujuk untuk rawatan iodin radioaktif untuk kali pertama telah diambil sebagai peserta kajian. Skan kelenjar tiroid menggunakan 'pertechnetate' dilakukan terlebih dahulu dan nisbah pengambilan 'pertechnetate' kelenjar tiroid ditentukan dan digunakan dalam pengiraan dos. Susulan dilakukan dan hasil rawatan ditentukan selepas tiga dan enam bulan. Data klinikal dianalisa menggunakan perisian IBM SPSS.

Keputusan: Seramai 95 orang peserta dengan min umur 46.0 tahun telah terlibat dan kebanyakan terdiri daripada wanita (76.8%) berbangsa Melayu (71.6%). Penyakit Graves adalah jenis hipertiroidisme yang paling kerap (67.4%) diikuti oleh penyakit goiter multinodular (30.5%) dan 52.6% daripada peserta mempunyai bengkakan leher gred dua. Seramai 91.6% daripada peserta telah dirawat dengan ubat carbimazole. Median nisbah pengambilan 'pertechnetate' adalah 18.0% dan median dos iodine radioaktif adalah 22.0mCi. Nisbah pengambilan 'pertechnetate' dan dos iodine radioaktif adalah berbeza berdasarkan saiz bengkakan leher ($p < 0.001$) dan juga mempunyai kaitan dengan ujian fungsi tiroid ($p < 0.001$). 82.1% daripada peserta mencapai eutiroid atau hipotiroid enam bulan selepas rawatan. Peserta dengan penyakit goiter multinodular mempunyai kadar kegagalan yang lebih tinggi berbanding peserta dengan penyakit Graves ($p = 0.032$). Seramai 75 peserta mengalami pengurangan saiz bengkakan leher dalam masa enam bulan dan lima peserta mengalami gejala 'hipotiroidisme sementara' sebelum hipertiroidisme berulang kembali selepas enam bulan.

Kesimpulan: Kaedah pengiraan dos ini telah menunjukkan hasil yang baik dengan kadar penyembuhan 74.7% pada tiga bulan dan 82.1% enam bulan selepas rawatan. Pesakit dengan penyakit goiter multinodular lebih cenderung untuk gagal rawatan berbanding dengan penyakit Graves.

ABSTRACT

Title: The Outcome Of A Calculated Radioiodine Dose Based On Pertechnetate Study In Treatment For Hyperthyroidism

Introduction: Apart from surgery and anti-thyroid drugs, radioactive iodine has been a mainstay of treatment for hyperthyroidism. There are two widely used methods for dose administration including empirical fixed dose and calculated dose. A recent meta-analysis supported that dose calculation is better than empirical fixed dose method. However, dose calculation by dosimetry or radioactive iodine thyroid uptake ratio at 24 hours can be tedious and may pose certain disadvantages to the patients and the provider. Pertechnetate thyroid scintigraphy is a simple nuclear imaging that can be completed on the same day and pertechnetate thyroid uptake ratio, which is determined from the scintigraphy, can be used to calculate the dose for radioactive iodine.

Objective: The aim is to optimise treatment efficacy and effectively treat hyperthyroid patients with a single radioactive iodine dose and this study is done to measure the efficacy of a calculated dose based on pertechnetate thyroid uptake ratio.

Methods: Hyperthyroidism patients referred for first radioactive iodine therapy were recruited as participants. Pertechnetate thyroid scintigraphy was done and pertechnetate thyroid uptake ratio was determined and used for dose calculation. Follow-up was done and the outcome of the treatment was determined at three months and six months. Clinical data was analysed using IBM SPSS software.

Results: A total of 95 participants with the mean age of 46.0 years were recruited and the majority consisted of Malay (71.6%) female (76.8%). Graves' disease was the most common type of hyperthyroidism (67.4%) followed by multinodular goitre (30.5%). Among the participants, 52.6% had grade 2 goitre and 91.6% were pre-treated with carbimazole. The median pertechnetate thyroid uptake ratio was 18.0% and the median radioactive iodine dose administered was 22.0mCi. The pertechnetate thyroid uptake ratio and radioactive iodine dose were significantly different based on goitre size ($p<0.001$) and correlated with thyroid function test ($p<0.001$). Six months after treatment, 82.1% achieved euthyroid or hypothyroid. Participants with multinodular goitre had higher failure rate than those with Graves' disease ($p=0.032$). Seventy-five participants had a reduction in goitre size within six months and five participants had transient hypothyroidism before relapsed at six months after treatment.

Conclusion: This calculated dose regime showed fairly good outcome with cure rate of 74.7% at three months and 82.1% at six months post treatment. Patients with MNG were more likely to relapse compared to Graves' disease.

Keywords: Hyperthyroidism, Graves' disease, Nodular Goitre, Nuclear Medicine, Radionuclide imaging, Pertechnetate, Sodium iodide

1.0 INTRODUCTION

Although radioactive iodine-131 (RAI) therapy is a mainstay of treatment for hyperthyroidism, various methods of administering RAI has been used in different centres and there is no consensus as to which method offers the greatest efficacy in treating hyperthyroidism patients, while keeping the radiation exposure to the minimum. This is further complicated by the numerous literatures available describing varied methods of dispensing RAI. A recent meta-analysis supported that dose calculation is better than empirical fixed dose method. However, dose calculation by dosimetry or radioactive iodine thyroid uptake ratio at 24 hours can be tedious. It is especially challenging in local setting where we have very limited facilities and resources, as Nuclear Medicine services are not available in every tertiary hospital. Patients need to travel afar to seek treatment and some may have difficulty in terms of logistics and finances, especially if repeated treatments are needed. In 2015, by using a fixed dose of 15mCi, 40% of the patients treated for hyperthyroidism in Nuclear Medicine Department, Hospital Pulau Pinang required repeated treatment. The repeated therapies use up part of the resources that can be channelled to other patients instead. Thus this study is conducted to find a treatment method that can cure hyperthyroidism with greater efficacy. A calculated dosing regime can potentially increase the treatment efficacy. By using pertechnetate uptake algorithm rather than RAI uptake, it offers greater convenience to the patients, as patients are not required to return the next day for dosimetry purpose and is better suited for local setting.

2.0 LITERATURE REVIEW

2.1 *Hyperthyroidism*

2.1.1 Definition and Demographics

Hyperthyroidism is a clinical state that results from high thyroid hormone action in the body due to excessive synthesis and secretion of thyroid hormones by the thyroid gland (Ross *et al.*, 2016). It is defined as subnormal serum thyrotropin or thyroid stimulating hormone (TSH) with increased serum triiodothyronine (T3) and/or tetraiodothyronine/thyroxine (T4) (Ross *et al.*, 2016). It is a common endocrine disease with the prevalence of 1.2% in the United States (Ross *et al.*, 2016). The prevalence is higher in areas with iodine deficiency compared to iodine sufficient areas (Vanderpump, 2011). Closer to home, the prevalence of hyperthyroidism was reportedly higher at 3.4% in a community based study in the west coast of peninsular Malaysia (Shahar *et al.*, 2015). The prevalence in female is much more common than male with the ratio of 4:1 (Vanderpump, 2011) and the prevalence is about 2% in women and 0.2% in men in UK (Gilbert, 2017). Most of the hyperthyroidism patients presented in the age between 20-50 years old (Sanjeeva *et al.*, 2015). Male patients were found to have a higher frequency of positive family history (Magri *et al.*, 2016). Other than familial, male are also associated with bigger thyroid size than female (Magri *et al.*, 2016).

2.1.2 Symptoms and Signs

The severity of the symptoms are moderately correlated with the biochemical severity (Gilbert, 2017) but poorly correlated with goitre size (Bonnema *et al.*, 2014). The effects of hyperthyroidism involves almost every system in the body (Ross *et al.*, 2016). Symptoms and signs of hyperthyroidism include palpitations, shortness of breath, tachycardia, arrhythmias, weight loss in spite of increased appetite, agitation, ophthalmopathy, tremor, muscle weakness, pretibial myxoedema, thyroid acropachy, sweating, heat intolerance, hair thinning and oligomenorrhoea (Kravets, 2016; Gilbert, 2017).

2.1.3 Aetiology

Graves' disease is the most common aetiology of hyperthyroidism followed by nodular goitre (Vanderpump, 2011; Rokni *et al.*, 2014; Ross *et al.*, 2016). Graves' disease is an autoimmune condition in which thyrotropin receptor antibodies (TRAb) stimulate the TSH receptors resulting in increased thyroid hormone synthesis and secretion. Somatic activating mutations of thyroid growth and hormone production regulating genes cause the formation of toxic adenoma. In multinodular thyroid disease, there's new nodule formations, growth of established nodules and development of autonomy over time (Ross *et al.*, 2016). There is also a mixed type hyperthyroidism where patients with features of multinodular goitre (MNG) could have positive TRAb which is suggestive of Graves' disease as well (Carlé *et al.*, 2011). Certain literature suggests that the natural course for Graves' disease is the eventual nodular formation due to the chronic stimulation of the thyroid gland (Kaniuka *et al.*, 2009).

2.2 *Diagnosis of Types of Hyperthyroidism*

The diagnosis of hyperthyroidism is based on biochemical test. Biochemical test will show suppressed serum TSH and elevated serum free T3 and/or free T4 (Dayan, 2001). In mild hyperthyroidism, serum T4 can be normal and only serum T3 may be elevated (Ross *et al.*, 2016).

Differentiating types of hyperthyroidism is primarily by clinical where Graves' disease presents with ophthalmopathy and diffuse goitre, whereas MNG or toxic adenoma will be apparent upon clinical examination of the neck where nodular goitre will be palpable (Ginsberg, 2003). Other biochemical and imaging modalities are used to help confirm the diagnosis. The TRAb will be positive in Graves' disease (Ross *et al.*, 2016). Thyroid scintigraphy, either by using RAI or technetium-99m (Tc-99m), can be done to distinguish the types of hyperthyroidism, especially if ophthalmopathy is absent (Ross *et al.*, 2016). For Graves' disease, it appears as homogenous uptake of the entire thyroid gland (Carlé *et al.*, 2011). MNG has heterogeneous uptake with at least 2 areas of enhanced uptake in thyroid scintigraphy (Carlé *et al.*, 2011). For solitary toxic adenoma, there will be a single area of increased tracer uptake in thyroid scintigraphy with low surrounding thyroid tissue uptake (Carlé *et al.*, 2011). Ultrasonography will show either a solitary or multinodular appearance in nodular goitre or diffusely enlarged gland in Graves' disease (Carlé *et al.*, 2011). Ultrasound Doppler flow as well as thyroid scintigraphy is useful to distinguish between Graves' disease and thyroiditis (Ross *et al.*, 2016).

As the diagnosis is mainly by clinical basis, the clinical palpation of the thyroid constitutes an important and indispensable tool in the work-up for hyperthyroidism. Clinical estimation of thyroid size yields a valid quantitative result and is cost saving. To objectively grade a patient's goitre, a classification by World Health Organisation (WHO) is

used where Grade 0 is when there is no palpable or visible goitre, Grade 1 is goitre that is palpable but no visible when neck in normal position and Grade 2 is goitre that is clearly visible when neck in normal position (World Health Organization, 2014). This is a technique that doesn't require training and can be done easily on a routine basis.

2.2.1 Pertechnetate Scintigraphy

Pertechnetate thyroid scintigraphy is a planar gamma imaging of the thyroid by using Tc-99m in the form of pertechnetate (Atkins, 1971). Pertechnetate is an anion and behaves similarly as iodide within the body. It is actively taken up by thyroid cells via the sodium iodide symporter but not organified (Silberstein *et al.*, 2012). Tc-99m is a metastable radionuclide and will decay into stable technetium by releasing pure gamma radiation with the energy of 140 keV (Ramos *et al.*, 2002). The half life of Tc-99m is 6 hours which is comparatively short and well suited for diagnostic imaging (Kidokoro-Kunii *et al.*, 2006). Additionally, it is easily available in every nuclear medicine centre as it is produced on-site by a small generator (Meller and Becker, 2002).

Patient undergoing the scan is injected with a small amount of pertechnetate and the patient is scanned using a gamma detector camera after 20 minutes. Pertechnetate thyroid uptake ratio (TcTU) can be calculated by using the planar image to gauge the severity of the hyperthyroidism (Schneider, 1979). The technique of calculation of TcTU based on imaging of thyroid gland was described by (Ramos *et al.*, 2002). Syringe counts before and after injection of radiopharmaceutical need to be obtained. The counts in the thyroid gland are determined by a region of interest (ROI) drawn along the borders of the gland and subtracted off the background counts by another ROI drawn just below the thyroid. The TcTU was calculated according to the ratio of background subtracted thyroid counts to the difference of post-injection syringe and pre-injection syringe counts.

The typical value of TcTU in patients with MNG ranges from 3.1% to 60% (Manohar *et al.*, 2013). The TcTU also correlates well to the thyroid's ability for iodine trapping via the expression of the sodium iodide symporter (Meller and Becker, 2002; Manohar *et al.*, 2013). Graves' disease will appear as diffuse uptake, MNG will appear as regions with focal increased or reduced uptakes and toxic adenoma will show a dominant hot nodule in the scintigraphy (Balon *et al.*, 2006). On the other hand, subacute thyroiditis will have generalised reduced uptake (Ziessman *et al.*, 2013).

2.3 Treatment Options

2.3.1 Medical

Medical treatment can be used for symptomatic relieve with beta-blockers especially for cardiovascular symptoms or to control hyperthyroidism using thioamides such as carbimazole, methimazole and propylthiouracil (Gilbert, 2017). American Thyroid Association (ATA) guideline recommended methimazole as the first drug of choice due to its potency and a more convenient daily dosing compared to propylthiouracil that is usually reserved for patients in their first trimester of pregnancy, thyroid storm or develop side effect with methimazole (Ross *et al.*, 2016). Carbimazole is a prodrug of methimazole and is widely used in this region. The potential adverse effects of thioamides include agranulocytosis and hepatotoxicity (Genovese *et al.*, 2013). However, the remission rate is low which is around 40% to 50% after 12-18 months of treatment (Burch and Cooper, 2015) and relapse rate after discontinuation of the drugs is reportedly 30% - 70% within the first year (Kravets, 2016).

2.3.2 Surgery

Surgical resection of the thyroid is more beneficial for large disfiguring goitre with compressive symptoms or those with suspicious thyroid nodule which is greater than 4cm or non-functioning on thyroid scintigraphy (Ross *et al.*, 2016). It has the advantage of being able to reduce the thyroid volume rapidly and completely. However, surgical complications will need to be considered especially in vulnerable group such as in the elderly with other co-morbidities and it may result in vocal cord paralysis in 1% of the patients (Burch and Cooper, 2015).

2.3.3 RAI Ablation

RAI therapy for hyperthyroidism has been widely used and accepted as the treatment of choice since the 1940's (Stokkel *et al.*, 2010; Silberstein *et al.*, 2012). This is the preferred choice of treatment in individuals with increased risks of surgical complications, previously operated neck, contraindicated for ATD or failed to achieve remission after ATD treatment (Ross *et al.*, 2016). The success rate was reported as high as 90% in France by using either fixed or calculated dosage (Bernard *et al.*, 2014). The potential side effects of RAI therapy include transient radiation induce thyroiditis that can cause post treatment hyperthyroidism and swelling, sialadenitis as well as transient hypothyroidism with eventual relapse (Bonnema and Hegedüs, 2012). The transient hypothyroidism phenomenon is postulated to be caused by thyroid stunning due to the low dose radiation or slow recovery of hypothalamic-pituitary axis (Bonnema and Hegedüs, 2012). Patients who develop hypothyroidism will require thyroxine supplement (Kravets, 2016).

2.4 RAI Ablation Therapy

2.4.1 Mechanism of Action

It utilises iodine-131 with the emission of beta radiation to induce cellular damage. Iodine-131 is a radionuclide that decays by emitting both gamma and beta radiation. Gamma radiation (364 keV) can be used for imaging and calculation of the radioiodine thyroid uptake ratio (ITU) and the beta radiation (606 keV) is responsible for the therapeutic effect with mean range in tissue of 0.4 mm. The physical half life of iodine-131 is 8.1 days (Stokkel *et al.*, 2010) and effective half life of approximately 6 days (Cepková *et al.*, 2014).

After ingestion, iodine-131 will be mostly taken up and accumulated by the thyroid gland in the form of iodide. The uptake is by active transportation into the thyroid follicular cells via the sodium iodide symporter. The iodide is then reduced to iodine and subsequently organified and incorporated into thyroid hormones and stored in active thyroid follicles (Stokkel *et al.*, 2010). Autonomously functional or 'hot' areas in thyroid scintigraphy will have more absorption leading to greater destruction and the effect will be reduced in the 'cold' areas in the scintigraphy (Kaniuka *et al.*, 2009).

The beta radiation emitted from the decay of iodine-131 will cause damage to the follicular cells by direct damage to DNA and free radical formation. This will result in cell apoptosis in the autonomous functioning thyroid tissues (Bonnema and Hegedüs, 2012).

2.4.2 Aim of Therapy

According to the practice guideline for therapy of thyroid disease with RAI published by Society of Nuclear Medicine and Molecular Imaging (SNMMI), the goal of therapy is to achieve non-hyperthyroid state which is either euthyroid or hypothyroid (Silberstein *et al.*, 2012). Based on European Association of Nuclear Medicine (EANM) guideline, the aim of treatment is to return patient to euthyroid state while minimizing the risks of developing hypothyroidism (Stokkel *et al.*, 2010).

Treatment with RAI will reduce the thyroid function and render patient euthyroid or hypothyroid in up to 90% of the patients after a single dose (Collier, 2012) and patients will usually respond to treatment in 4 to 8 weeks with hypothyroidism frequently occurring between 2 to 6 months (Ross *et al.*, 2016). It is also able to reduce the thyroid volume by 35-50% within one to two years (Bonnema *et al.*, 2014). The size reduction can occur gradually, up to 50% of the patients in 6 months and 70% in 1 year regardless of diagnosis (Peters *et al.*, 1996).

It is recommended that if a patient remains hyperthyroid after 6 months, second dose of RAI may be given but at the expense of more radiation dose to the patient (Ross *et al.*, 2016). Although hypothyroidism has been reported as a complication in some studies, it is a targeted endpoint especially for old age patients with cardiac complications to achieve long term hypothyroidism with a single dose to prevent exacerbation of symptoms (Şakı *et al.*, 2015).

2.4.3 Methods to Determine RAI Dose

Each centre has its own set of protocol, ranged from meticulously calculated dose to empirical fixed dose of RAI that varied from one to another (Erem *et al.*, 2004; Cepková *et al.*, 2014). ATA guideline recommended that patient be rendered hypothyroid using a single dose to avoid retreatment, either by using fixed dose or by calculated dose. There is no consensus to which treatment yields the best response with the least radiation dose to the patients (Kusumahstuti *et al.*, 2014).

2.4.4 Fixed Dose Method

ATA guideline stated that fixed dose ranging from 10 to 20 mCi can be given to render patient hypothyroid (Ross *et al.*, 2016). Collier reported that using a fixed dose between 10 mCi to 15 mCi for Graves' disease in Scotland has a success rate of 90% (Collier, 2012). In Hasan Sadikin Hospital, the reported success rate for fixed dose 8 mCi was 72% in 3 months and 83% in 6 months (Kusumahstuti *et al.*, 2014).

There are various clinical considerations used to adjust the fixed dose regime according to different clinical situations. A higher fixed dose will achieve maximum cure rate but at the expense of higher radiation dose and inevitable hypothyroidism (Stokkel *et al.*, 2010). When compared fixed high dose vs fixed low dose, patients treated with high dose were 18.1% more likely to be cured although the risk of permanent hypothyroidism was 23.9% higher in fixed high dose (Rokni *et al.*, 2014).

In a centre in Hong Kong, 8 mCi was used for most patients and 10 mCi was given to patients with complications related to thyrotoxicosis such as atrial fibrillation, heart failure and periodic paralysis and the success rate was only 63% after one year (Yau *et al.*,

2009). A graded fixed RAI dosing for Graves' disease with the dose adjustment based on the absorbed dose and thyroid volume was used in Poland and the success rate was reported to be 88% (Szumowski *et al.*, 2015).

2.4.5 Calculated Dose Method

The advantage of calculated dose compared to fixed dose is that calculated dose offers better cure rate. According to a recent meta-analysis, calculated dose has a 9.6% higher rate of curing hyperthyroidism and 0.3% less rate of developing permanent hypothyroidism with a single dose when compared to fixed dose (Rokni *et al.*, 2014). In a randomised control trial comparing fixed high dose (22.5 mCi), fixed low dose (13 mCi), calculated low dose (90 – 100 µCi/g) and calculated high dose (180-200 µCi/g) for toxic nodules, the success rate is higher in calculated high dose and low dose compared to both fixed dose, favouring the calculated dose regime (Zakavi *et al.*, 2009). By using dosimetric calculation for dosage, the success rate was 82% in a study done in Italy (Schiavo *et al.*, 2015) while in another study involving various types of hyperthyroidism, the overall success rate was 77% using calculated dose (Schneider *et al.*, 2014).

For the dose calculation, the formulation can be based on the target absorbed dose or the target delivered dose per thyroid mass, corrected by the ITU. The widely used dose calculation in the SNMMI guideline is based on how much activity that is delivered to the thyroid gland,

$$\text{Activity (}\mu\text{Ci)} = \frac{\text{Gland weight (g)} \times \text{Activity delivered (}\mu\text{Ci/g)}}{24\text{-hour ITU (\%)}}$$

where 'gland weight' is the estimated weight of the thyroid gland, 'activity delivered' is the desired activity to be delivered to each gram of the thyroid mass and '24-

hour ITU' is the percentage of RAI uptake by the thyroid measured after 24 hours (Silberstein *et al.*, 2012). For the dose calculation, thyroid volume estimation can be done by magnetic resonance imaging (MRI), computed tomography (CT) or ultrasonography (Bonnema and Hegedüs, 2012) and 24-hour ITU can be estimated either by thyroid probe or thyroid scintigraphy (Mumtaz *et al.*, 2009; Ross *et al.*, 2016).

Based on ATA guideline, a calculated dose by giving 50-200 $\mu\text{Ci/g}$ of thyroid tissue corrected for RAI uptake should be given to patient in treatment of hyperthyroidism (Ross *et al.*, 2016). Evidence had shown that the dose delivered should be more than 150 $\mu\text{Ci/g}$ to achieve hypothyroid state (Ross *et al.*, 2016). In a study where the author used the formula for calculated dose based on thyroid volume and 24-hour ITU to deliver 160 $\mu\text{Ci/g}$, high cure rate using a single dose is reported with less than 10% of patients needing further RAI dose (Iagaru and McDougall, 2007). In another retrospective study, the author also found higher cure rate when the dose delivered was above 160 $\mu\text{Ci/g}$ (Cepková *et al.*, 2014). Dora *et al.* did a randomised control trial comparing efficacy of RAI between 200 $\mu\text{Ci/g}$ and 250 $\mu\text{Ci/g}$, and the author found that, although by increasing the delivered dose by 25%, the difference in efficacy was not statistically significant, although the success rate for patients received 250 $\mu\text{Ci/g}$ was 66% which is 6% higher than those who received 200 $\mu\text{Ci/g}$ (Dora *et al.*, 2013).

The limitation of using 24-hour ITU in the calculation of dose is that it requires patients to return to the hospital the next day or be warded overnight and this poses a logistic issue for patients especially in our local setting. Using ultrasonography for the volume estimation also has its limitations though it gives important morphological changes within thyroid gland where focal autonomy can be seen as a circumscribed nodule with hypoechoic appearance in 70% of the patients. However, the positive predictive value of the finding is low as hypofunctioning adenomas and regressive changes may have similar appearance (Meller and Becker, 1999). Furthermore, in many cases the autonomous target volume may differ from the total thyroid volume especially in MNG

where there is a mixture of autonomous and non-autonomous functioning nodules (Reiners and Schneider, 2002).

2.4.6 Calculation Method Based on TcTU

Due to the limitation of ultrasonography described above, TcTU was investigated as a tool to determine the volume of autonomous nodules as TcTU correlated well with the volume based on ultrasonography and can be regarded as a measure of functional volume (Reiners and Schneider, 2002). It was found that TcTU approach can better determine the amount of autonomous functioning thyroid tissue which is the better estimate for tissue volume that will take up and accumulate RAI for more effective treatment (Yüksel *et al.*, 2011). Also, there is strong correlation found between TcTU at 20 minutes and ITU at 24 hours (Smith *et al.*, 1990; Meller and Becker, 1999).

Therefore a modification of the calculation algorithm to be based on TcTU was investigated by a group of researchers. Four published algorithms of RAI dose calculated using TcTU to estimate for the autonomous volume,

Joseph 1977 (volume = $8.33 \times \text{TcTU} - 6.67$),

Kreisig 1992 (volume = $10 \times \text{TcTU} - 9.3$),

Emrich 1993 (volume = $5 \times \text{TcTU} + 0.6$) and

Joseph 1994 (volume = $2.88 \times \text{TcTU} + 0.09$)

have been evaluated by Gotthardt *et al.* in 2003. In the study, Marinelli's formula was used,

$$\text{Activity} = \frac{\text{Target dose} \times \text{Volume}}{1.5 \times \text{Effective half-life} \times 24\text{-hour ITU}}$$

where the effective half life was taken as 6 days for iodine-131 and 24-hour ITU was given by the function of $7.5 \times \text{TcTUs} + 7.5$, thus

$$\text{Activity (mCi)} = \frac{\text{Target dose} \times [8.33 \times \text{TcTU (\%)} - 6.67]}{67.5 \times \text{TcTU (\%)} + 67.5}$$

Their study had shown that among the four algorithms, Joseph's algorithm in 1977 was the most reliable approach for calculation of thyroid volume using TcTU and the treatment efficacy was more than 92% by using the RAI dose calculated from the TcTU adapted formula (Gotthardt *et al.*, 2003). By using the TcTU calculation approach for the RAI dose, Reinhardt *et al.* reported treatment success rate of 94% and this approach may be applied to goitres with disseminated, multifocal and unifocal thyroid autonomy (Reinhardt *et al.*, 2002; Reinhardt *et al.*, 2006).

The other benefit of applying the algorithm using pertechnetate thyroid scintigraphy is being able to provide logistic convenience to patients, as the procedure is done on the same day within an hour, with better dosimetry and image quality compared to 24-hour radioiodine thyroid scintigraphy that requires patients to return to the facility after 24 hours. The scan has no significant side effects as pertechnetate is cleared rapidly from the body and has high safety profile. The effective dose for a pertechnetate thyroid scintigraphy is only 0.013 mSv/MBq compared to effective dose of iodine-131 thyroid scintigraphy of 11 mSv/MBq (Balon *et al.*, 2006). Pertechnetate thyroid scintigraphy prior to the administration of RAI therapy also serves as a screening tool as low uptake will lead to treatment failure and patients with low uptake are not suitable candidates for RAI therapy (Iagaru and McDougall, 2007). It can also detect any suspicious dominant cold nodules which warrant additional work up for possibility of thyroid carcinoma (Ross *et al.*, 2016).

2.4.7 Other Factors Affecting Treatment Outcome

There are several factors that can affect the treatment outcome apart from the type of treatment regime described above. An author had found that the male gender with age younger than 40 years old has reduced chance of cure (Allahabadia *et al.*, 2000). In a centre in Poland, the highest relapse rate was found in patients with thyroid gland more than 50 mls (Szumowski *et al.*, 2015). In a centre in Hong Kong, the main factor for treatment failure was large goitre size and high pretreatment T4 level (Yau *et al.*, 2009). In a study done in 2014, patients with more severe thyroid function had increased treatment failure rate (Schneider *et al.*, 2014). The type of hyperthyroidism also affects the treatment efficacy as a study had shown that the positive outcome rate of MNG is lower than Graves' disease (Körber *et al.*, 2001). This is due to the steal phenomenon in MNG where ATD diverts the RAI from the autonomous nodules to the rest of the thyroid tissue (Bonnema and Hegedüs, 2012). Pretreatment with carbimazole and propylthiouracil are also known to reduce RAI treatment efficacy (Hancock *et al.*, 1997; Shivaprasad and Prasanna Kumar, 2015). Continuous treatment with carbimazole during and after RAI therapy was shown to be significantly associated with poorer outcome (Bonnema *et al.*, 2006). Pretreatment with propylthiouracil prior to RAI therapy may reduce the cure rate at 1 year by approximately half (Bonnema *et al.*, 2004).

2.5 RAI Therapy in Malaysia

2.5.1 Current Practice

The routine RAI therapy practice in Hospital Pulau Pinang for hyperthyroidism patients is based on a fixed empirical dose of 15 mCi. Diagnosis is based on clinical and biochemical test. Neck ultrasonography and thyroid scintigraphy is not routinely done for the patients. Thus thyroid size is estimated by clinical palpation. Patients will need to stop taking ATD for 1 week and avoid iodine containing food or substances for 2 weeks duration prior to the RAI therapy. After the therapy, the patients are given regular follow-ups and thyroid function test (TFT) are monitored during each visit. If a patient remains hyperthyroid 6 months after the initial treatment, patient is advised for a second dose of RAI.

2.5.2 Treatment Outcome

Majority of the hyperthyroidism patients in Malaysia were females from the Malay ethnic group in their 5th decades of life (Shahar *et al.*, 2015). Also, from the background data search obtained from the database of Nuclear Medicine Department, Hospital Pulau Pinang from March 2015 to March 2016, the mean age of the patients was 47 years old $\pm$ 14.45 years and 75% of the patients were female. Majority were Malays (63.5%) followed by Chinese (29.1%) and Indian (3.4%). Sixty-five patients (43.9%) were referred for Graves' disease, 35 patients (23.7%) were referred for multinodular goitre and the rest were referred as hyperthyroidism with indeterminate cause. The median duration of disease was 48 months with interquartile range (IQR) of 24 to 105 months and 97.3% of

them were on carbimazole. The success rate at 3 months was 54.1% with 26 patients achieving euthyroid state and 54 patients became hypothyroid. The success rate at 6 months was 59.1% with 19 euthyroid patients and 67 hypothyroid patients.

2.6 Conclusion of Literature Review

In conclusion, hyperthyroidism is an endocrine disorder mostly affecting female. Graves' disease is the commonest aetiology. The aim of RAI therapy is to active non hyperthyroid state, either euthyroid or hypothyroid and if patient remains hyperthyroid after 6 months of therapy, second dose of RAI may be given. Recent meta-analysis showed that calculated dose is better than fixed dose regime. Adequate delivered dose of more than 150 $\mu\text{Ci/g}$ should be given to achieve remission but delivered dose higher than 200 $\mu\text{Ci/g}$ did not significantly increase the success rate. TcTU correlated well with ITU and is useful as a measurement of functional volume. A calculated dose using TcTU algorithm offers greater convenience and is able to achieve high success rate. Among the 4 different algorithms investigated by Gotthardt *et al.* in 2003, Joseph's algorithm (1977) had the highest success rate and was recommended to be used.

3.0 RATIONALE/BENEFITS OF THE STUDY

This research is conducted in search to optimise the treatment efficacy by using a calculated dose based on TcTU and to effectively treat patients with hyperthyroidism with a single RAI dose. By using the calculated dose, this has the advantage to effectively render patient euthyroid or hypothyroid with a single dose and reduce the possibility of repeated therapy to minimise radiation exposure, based on 'As Low As Reasonably Achievable' principle. Calculation of the dose by using TcTU is more time saving, cost efficient, more convenient for patients and subjected to lower radiation dose compared to using ITU.

3.1 Aim

To effectively treat hyperthyroid patients with a single RAI dose using calculation based on TcTU.

3.2 Objectives

3.2.1 General Objective

- To measure the efficacy of a calculated dose based on TcTU in the management of patients with hyperthyroidism

3.2.2 Specific Objectives

- To look at the demographics of patients with hyperthyroidism who came for RAI therapy
- To determine the TcTU for the calculation of dose
- To calculate the administered RAI dose based on the TcTU
- To determine the outcome of RAI therapy at 3 months and 6 months post treatment

3.3 Hypothesis Statements

- Null hypothesis: The success rate of the first RAI therapy after 6 months of treatment = 92% (based on the success rate in a paper by Gotthardt *et al.*, 2003).
- Alternate hypothesis: The success rate of the first RAI therapy after 6 months of treatment $\neq$ 92%.

4.0 METHODOLOGY

4.1 Study Design, Study location and Study Period

A single arm randomised prospective study was carried out in the Department of Nuclear Medicine, Hospital Pulau Pinang, Pulau Pinang, Malaysia from the period of March 2016 to September 2017.

4.2 Study Sample

Patients with hyperthyroidism who underwent RAI therapy in the northern states of peninsular Malaysia including Pulau Pinang, Kedah, Perlis and northern Perak were the reference population. Those who were referred to the Nuclear Medicine Department, Hospital Pulau Pinang for RAI therapy were the source population. The patients with hyperthyroidism who came to Nuclear Medicine Department, Hospital Pulau Pinang for RAI therapy were the sampling population and the study participants were those who consented to participate in this study and fulfilled the inclusion and exclusion criteria. Refer APPENDIX B for sample size calculation.

4.3 Inclusion and Exclusion Criteria

4.3.1 Inclusion Criteria

- Patients aged above 18 years old
- Patients referred for first RAI therapy for hyperthyroidism

4.3.2 Exclusion Criteria

- Patients who were pregnant or breastfeeding
- Patients with history of thyroid surgery
- Patients referred for RAI therapy for thyroid cancer

4.4 Data Collection

All referrals for RAI therapy were screened by the principal investigator (PI). Those who fulfilled the inclusion and exclusion criteria were selected to participate in this study and informed consents were taken by the PI.

All participants were given counselling and provided with a copy of the departmental leaflet containing instructions and preparation checklist before the thyroid scintigraphy and RAI therapy (APPENDIX C). Participants were asked to withhold ATD for a week and avoid substances with high iodine content including seafood, sea salt, cough mixture, Lugol's iodine and multivitamins for two weeks prior to the appointment date (Amaral and Michaud, 2001).

On the day of the appointment, all the participants were clerked and examined by the PI to ensure compliance to the preparation. Clinical data as well as written consent

were obtained from the participants (APPENDIX D and E). Blood for TFT was taken and pertechnetate thyroid scintigraphy (refer APPENDIX F for full department protocol) was performed on the same day prior to RAI therapy and TcTU was calculated by camera based method using standard software. The planar pertechnetate scintigraphy images were interpreted by a nuclear medicine specialist for the diagnosis. Dose for the RAI therapy was then calculated by the PI and the dose was rechecked by the dispensing pharmacist before administered to the participants.

All participants were treated on out-patient basis and were allowed to go home after RAI administration with radiation safety advice (International Atomic Energy Agency, 2009; Sisson *et al.*, 2011). ATD was resumed a week after RAI treatment for a month to prevent clinical exacerbation of hyperthyroidism (Ross *et al.*, 2016). Follow-up reviews were done at 3 months and 6 months post therapy.

Study data information sheet was used for data compilation (APPENDIX G). Demographic data such as age, ethnic and gender, goitre size, prior laboratory and ultrasonography results, diagnosis, duration of disease, ATD pretreatment, TFT done before and after treatment, thyroid scintigraphy findings and administered dose were evaluated.

4.4.1 Thyroid Size Estimation

Thyroid gland size was estimated by clinical palpation based on World Health Organization (WHO) classification (World Health Organization, 2014),

- Grade 0: No palpable or visible goitre
- Grade 1: Goitre that was palpable but not visible when neck was in normal position
- Grade 2: Goitre that was clearly visible when neck was in normal position

4.4.2 Thyroid Scintigraphy and Uptake

Tc-99m in the form of pertechnetate was used as the radiopharmaceutical tracer and 5 mCi injected intravenously. Planar images were acquired 20 minutes after the injection using single photon emission computed tomography scintillation gamma camera equipped with a low-energy, high-resolution and parallel-hole collimator (E.CAM, Siemens Medical Solutions) with energy peak at 140 keV and 20% energy window. Scan was done in supine position with neck extended and supported by pillow placed under shoulder. Pre-injection syringe and post-injection syringe counts as well as anterior images of the neck were acquired for 200 seconds. The TcTU was calculated by camera-based method using standard software. The method for the calculation of TcTU was as previously described by Ramos *et al.* (2002). Refer APPENDIX F for the complete department protocol for thyroid scintigraphy.

4.4.3 Calculation of RAI Dose

The RAI dose was calculated based on the formula in the paper by Gotthardt *et al.* (2003) and Joseph's algorithm was chosen as it was showed to have the highest success rate among the 4 algorithms. The desired delivered activity was set at 200 as recommended by ATA guidelines as it was shown to have good treatment efficacy (Silberstein *et al.*, 2012; Dora *et al.*, 2013).

$$\text{Dose (mCi)} = \frac{200 \times [8.33 \times \text{TcTU (\%)} - 6.67]}{67.5 \times \text{TcTU (\%)} + 67.5}$$

4.4.4 Diagnosis for The Types of Hyperthyroidism

The diagnosis for the different types of hyperthyroidism was made according to the features in an article published by Carlé *et al.* (Carlé *et al.*, 2011).

- Graves' disease:

Patients with clinical presence of ophthalmopathy and/or positive TRAb with diffuse goitre on palpation. Imaging diagnosis was by appearance of homogenous uptake of the entire thyroid gland on thyroid scintigraphy.

- MNG:

Patients with nodular goitre on palpation or nodular appearance in ultrasonography or heterogeneous uptake with at least 2 areas of enhanced uptake in thyroid scintigraphy.